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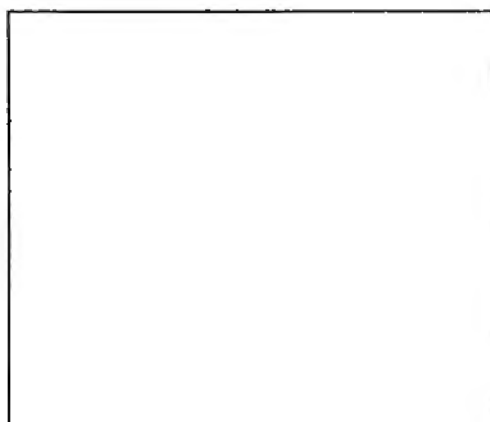
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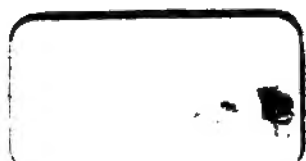




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**A GUIDE**  
**TO THE**  
**QUALITATIVE AND QUANTITATIVE**  
**ANALYSIS OF THE URINE**

**DESIGNED FOR**  
**PHYSICIANS, CHEMISTS AND PHARMACISTS**

**BY**  
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**WITH A PREFACE BY**  
**PROF. DR. R. FRESENIUS**

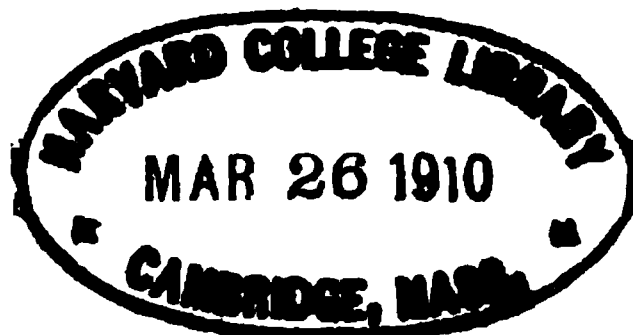
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Pres. C. W. Eliot

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## PREFACE TO THE FIRST EDITION.

---

MR. C. NEUBAUER, assistant in my laboratory, having been requested by a number of the physicians of the city, has given them a series of lectures on the analysis of the urine, which has recently undergone complete remodelling, and is constantly assuming a greater importance.

These lectures gave the first origin to this book. Since Neubauer has labored with great diligence on the basis of the newest investigations, and has himself tried all of the accepted methods, it will prove very welcome both to physicians and to pharmacists and chemists who aid them, and will prove a reliable guide to urinary analysis.

The publisher has spared neither cost nor pains in preparing the book ; all apparatus is illustrated by fine wood-cuts, and the appearances of the most important normal and abnormal constituents of the urine are depicted in truly excellent plates, so that the work is to be highly recommended in this respect.

PROF. DR. R. FRESENIUS.

WIESBADEN, April 5, 1854



## PREFACE TO THE SEVENTH EDITION.

---

IN revising the present seventh edition of my Analysis of the Urine, I have honestly tried my best to take account of the progress of science. In the first three divisions, therefore, I have carefully added all reactions and methods which have been approved by myself or others. Among the new additions are the chapters on brencatechin, acetone, and the two pathological coloring matters discovered by Baumstark, urobilinogen and urobilinogen.

The fourth division, which treats of the accidental constituents of the urine, has been considerably enriched. It is evident, at first sight, how important are the physiological and pathological changes which substances undergo in their passage through the system, and, therefore, we gladly see that a considerable activity has been developed in this part of urinary analysis during the last few years.

Also the second part, which includes the methods of quantitative analysis, has been considerably enlarged. I mention the handy and delicate method of determining the specific gravity by the Mohr-Westphal balance, the Knop-Hüfner method of determining the urea, which is very good and easily performed in many cases, and also Bunge's modification of Bunsen's method for the same purpose, which, according to recent experience, is found to be indispensable in many cases where Liebig's method failed. Also, I could not refuse a place to the new method of determining chlorine by Volhard and Falk, which is not inferior to Mohr's in accuracy. In the optical estimation of sugar, I have considered, besides the polariscope of Ventzke-Soleil, that of Wild, which has decided advantages over the former, and admits of an accuracy which I,

at least, have been unable to attain with the apparatus of Ventzke-Soleil. Also, the estimation of sugar from the difference in specific gravity before and after fermentation, will not be entirely unwelcome to many physicians who are not conversant with volumetric analysis, and who do not have the expensive optical apparatus at their command. Lastly, I mention the new method of determining iodine by Hilger, and the method of Salkowski for estimating uric acid.

With regard to the formulas which I use, I have given them both in the old and new nomenclature, and have designated the new atomic weights by large type and crossed capitals, to do justice to the old as well as the new friends of my book.

I have received from different sources reprints of articles on the subject of urinary analysis, by which the review of the chemical, medical, and physiological current literature of the scattered material has been rendered essentially easier. I most heartily thank all who have aided me in this labor, and, at the same time, beg that they will be as kindly thoughtful in the future.

May this new edition receive the same friendly acceptance and favorable criticism which has been its lot before.

C. NEUBAUER.

WIESBADEN, October, 1875.

## REVISER'S PREFACE.

---

THE want of a practical manual and suitable text-book upon the analysis of the urine in the English language has long been felt. This want has, during the past few years, been partly supplied by Dr. Tyson's excellent little "Guide to the Practical Examination of Urine," which, however, is not, and does not pretend to be, a complete manual upon urinary chemistry. The medical student and practitioner need to know something more than simply the methods which are required to obtain a knowledge of the chemical composition of the urine. They should be able to infer from it, to a certain extent, the general condition of the patient whose urine is examined, and it is hoped that the present work may accomplish for the English reader, what the original has for the German student, viz., show him exactly what inferences may be drawn from a knowledge of the chemical composition of the urine, and in what way and to what extent a knowledge of the changes going on within the body may be learned by examining the urine.

There is no book in the English language which treats the subject of urinary chemistry in so thorough and scientific a manner, and in none is the material so arranged as to be readily available to both student and practitioner. The separation of the book into two distinct parts, the first by Dr. Neubauer being strictly chemical, and the second by Dr. Vogel being chiefly medical, adds much to its value as a book of reference for both the chemist and physician.

Since the former translation of Neubauer and Vogel, published by the New Sydenham Society in 1863, such vast progress has been made in the domain of organic and physiological chemistry, that the original work has passed through four editions, and the 1863 translation by no means represents the present standpoint of urinary chemistry. The present (seventh) edition contains the most recent advances culled from the current literature of the day.

Some difficulties have been met with in the translation, which all who have done the same kind of work can appreciate. The translation has been made as literal as possible to be consistent with clearness, and elegance of style has not been aimed at.

Boston, 1879.

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BY C. NEUBAUER.

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## INTRODUCTION.

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WITH the rapid development of chemistry in the last few decades, its reaction upon other arts and sciences has been manifest. Where do we find now a rational manufacturer or farmer who does not constantly appeal to chemistry, so much is he impressed with its importance? Who can question the important services it has rendered medical science already? Physiology and pathology owe a great part of their rapid growth of late years to the development of this young science. How simple have the processes of respiration and nutrition become, since chemistry with balance and weights has determined the metamorphosis! Physiologists and physicians have long recognized the importance of the earnest study of this process, and have turned their attention to the investigation of the rapidity of the transformation of tissue.

Zoöchemical analysis, through the earnest zeal of so many observers, has naturally flourished and rapidly developed. It soon taught that the urine was the special storehouse for the decomposition products of animal tissues, and that its study would give conclusive information concerning the organic processes in the diseased as well as in the healthy body. This secretion has, therefore, been investigated with great diligence, since the first origin of zoöchemical analysis. Many substances were discovered in it, and many appearances observed which permitted conclusions to be drawn concerning the function of the organism.

Unfortunately, until within a short time, the analysis of the urine was a very protracted and laborious undertaking, and could not be performed by practising physicians. How different has this become in modern times! It is now possible for medical men, furnished with the simplest and most accurate methods,



to test the urine at the bedside in a short time, either for the discovery of a few abnormal constituents, or for determining the quantity of several of the normal constituents. If, in addition, the microscope be used rationally, all the conditions are given for an accurate determination of the changes in the organism from the composition of the urine.

In the following pages I shall first give a description of normal urine, and at the same time call attention to the peculiar changes which it undergoes in the acid and alkaline fermentation. The chemical properties of the normal and abnormal, organic and inorganic constituents is added to the first part, in which I shall pay special attention to the appearances of each under the microscope.

The second part treats exclusively of the different quantitative methods, with a detailed account of the necessary precautions, manipulations, and contingent modifications.

The third part, on the other hand, contains a practical guide to the qualitative and quantitative examination of the urine and its sediments, in accordance with the present standpoint of chemistry.

The following is a summary of the entire contents :

#### I. DIVISION.

1. Physical and chemical properties of normal urine.
2. Normal constituents.
  - a. Organic.
  - b. Inorganic.
3. Abnormal constituents.
4. Sediments.
5. Accidental constituents.

#### II. DIVISION.

Quantitative estimation of the various organic and inorganic constituents.

#### III. DIVISION.

1. Practical guide to qualitative analysis.
  2. Recognition of sediments under the microscope.
  3. Practical guide to quantitative analysis.
  4. Practical guide to the approximate quantitative estimation.
- Analytical notes.

# PART FIRST.

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A TREATISE

ON THE

CHEMICAL AND MICROSCOPICAL CHARACTERISTICS AND  
PROPERTIES OF THE URINARY CONSTITUENTS ;

TOGETHER WITH A

GUIDE TO THE QUALITATIVE AND QUANTITATIVE CHEMICAL  
EXAMINATION

OF NORMAL AS WELL AS ABNORMAL URINE.

BY

CARL NEUBAUER.



# ANALYSIS OF THE URINE.

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## DIVISION FIRST.

### I. PHYSICAL AND CHEMICAL PROPERTIES OF NORMAL URINE.

#### § 1.

It is an established fact that the urine, physiologically considered, is a true secretion by organs specially adapted for that purpose, the kidneys. We find in it, in the form of soluble nitrogenous and saline compounds, those elements which by transformation have become useless to the economy.

Generally considered, the constituents of normal urine may be regarded principally as the products of metamorphosis of the animal tissues, etc. Most important are the organic nitrogenous constituents of the urine: urea, uric acid, hippuric acid, oxaluric acid, kreatinin and xanthin, besides the coloring and extractive matters. Of these in human urine, urea occupies the first place; it is the most important product of retrograde metamorphosis of the nitrogenous constituents of the body, from which it is formed by the oxidizing power of the organism in a manner yet unknown, since hitherto it has not been possible, in spite of many attempts, to produce urea artificially by the action of energetic oxidizing agents \* on protein substances.

Indeed, several facts indicate that, in the oxidation of the

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\* The repeated assertion of Bechamp that urea may be formed by the action of permanganate of sodium on protein bodies has not been confirmed by Städeler, Loew, and myself.

different varieties of albumen, in the economy, its nitrogen is not directly converted into the form of urea, but previously a number of intermediate products are formed, which, by further decomposition, furnish urea. Thus, O. Schultzen and Nencki \* found that leucin and glycocoll, even when rapidly absorbed into the economy in large amounts, were eliminated in the form of urea; and, according to the experiments of Von Knieriem,† ammonium chloride, asparagin, and asparagic acid, which latter was discovered by Radziejewski and E. Salkowski to be the product of the digestion of fibrine by the pancreatic ferment, likewise cause an increase of urea in the urine. In the same way, in those diseases in which oxidation is much impaired, as acute yellow atrophy of the liver, etc., very large quantities of leucin and tyrosin are found in the urine, substances which Kühne showed were formed in large amount by the action of the pancreatic ferment on albuminates, while, in such cases, urea often wholly disappeared, and at the same time, paralactic acid, which, under normal conditions so readily oxidizes, was largely present.‡

Besides the above-named bodies, the mineral constituents of the blood, which have become physiologically useless, as well as many other substances entering into the economy, which are unnecessary for the process of metamorphosis, or are even injurious, are discharged with the urine, either unchanged or after chemical transformation. Finally, we must mention water, by the separation of which the kidneys regulate its amount in the blood, which is thus kept at a tolerably constant density. Normal urine, then, appears to be a very complex fluid, whose composition varies according to different classes of animals.

Food exercises an undoubted influence on the composition of the urine, which is distinctly proved in the carnivora and herbivora. The urine of the former does not differ essentially from that of human beings. In the fresh state it is clear, light yellow, of unpleasant odor, bitter taste and acid reaction. The amount of urea is considerable, while the uric acid often entirely disappears, but soon increases, however, when

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\* Berichte der deutsch. chem. Gesellschaft, 1869, p. 566.

† Zeitschrift für Biologie, Band 19, p. 263.

‡ O. Schultzen und L. Riess: *Über acute Phosphorvergiftung und Leberatrophie.*

the beasts are deprived of their free exercise, as when confined in cages.

Entirely different from this is the urine of the herbivora, which is characterized by its constant turbidity, alkaline reaction, and also by its considerable richness in carbonates of the alkalies and alkaline earths. It often contains a tolerable amount of urea, but is for the most part rich in hippuric acid: uric acid is often wholly absent, and also the phosphates occur in very small amount. Calcic oxalate, together with crystallized calcic carbonate, is always found in the sediment of this urine.

The influence of food on the composition of the urine appears most distinctly when herbivora are forced to digest only animal food, or when they are made to fast for a long time, so that life is maintained entirely at the expense of the constituents of their own bodies. The urine thereby very soon loses its alkaline reaction, it becomes acid, urea appears in considerable quantity, the sediment of calcic carbonate disappears, and uric acid in appreciable quantity is found. The urine, therefore, assumes the same character as that of the carnivora, a fact which can readily be demonstrated on rabbits.\* Exactly the reverse occurs when carnivora are fed on a purely vegetable diet.

The urine of birds, reptiles, etc., differs entirely from that of the mammalia, whence it must be inferred that the organization of these animals has a decided influence on the composition of the urine.

Normal human urine shows, in general, more resemblance to that of the carnivora. Freshly passed it appears clear, of a light amber-yellow color, distinctly acid reaction, bitter, salty taste, and peculiar aromatic odor. Städeler, in his great work, was the first to throw some light on the odorous matters in the urine, which work was chiefly on cow's urine, but included human urine also. By distillation of large quantities he succeeded in recognizing a series of peculiar volatile acids as the cause of the odor in cow's urine; among these are to be mentioned carbolic acid, also taurylic, damoluric, and damolic acids. Human urine contains very much smaller amounts of these acids, and

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\* *Annal. der Chemie und Pharm.*, Band 90, p. 106.

it is only by taking very large quantities for examination that we can succeed in distinctly recognizing carbolic acid by its characteristic reactions. But whether these acids, and especially the carbolic acid, either free or combined with an alkali, are really constituents of normal urine, appears, from the more recent investigations of Buliginsky \* more than doubtful, since these rather indicate that the carbolic acid is produced by the action of mineral acids on evaporated urine from a substance hitherto entirely unknown.

The specific gravity of normal human urine varies according to age and sex, constitution of body, and food, and varies from 1,005 to 1,030.

There has been much dispute concerning the cause of the constant acid reaction of normal human urine, which, according to the investigations of Klüpfel,† is considerably increased by strenuous muscular exercise, while Sawicki ‡ could not determine that rest or work had any influence on its acidity; finally Liebig proved that the acidity arose chiefly from the acid phosphates. Since the experiments of Lehmann, there can be no doubt that in many cases free hippuric and lactic acids are found in the urine, which naturally contribute to the acid reaction. Under all circumstances the quantity as well as the quality of the food ingested has the greatest influence on the acidity of the urine.

Since a solution of hyposulphite of sodium is immediately rendered turbid by a trace of free acid from the separated sulphur, Huppert § made use of this salt with the best result to detect the presence of free acid, together with the acid salts, in a urine which has an acid reaction. Urea, which behaves like an ammonium compound with acids, and also, according to Lehmann's experiments, enters into fixed combinations with phosphoric acid, is, according to Huppert, not able to prevent the destructive action of acids on the hyposulphite of sodium, but only retards it. It is, therefore, to be considered that every urine, which, upon the addition of a solution of hyposulphite of sodium, immediately becomes cloudy, contains free acids—free

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\* Hoppe-Seyler, med. chem. Untersuchungen, Heft 2, p. 234.

† Hoppe-Seyler, med. chem. Untersuchungen, Heft 3, p. 412.

‡ Pflüger's Archiv, Band 5, p. 285.

§ Archiv der Heilkunde, Band 8, p. 354.

acids in the sense that the collective bases in the urine, urea, etc. included, are not sufficient to form with them acid salts. If the separation of sulphur occurs only after a long time, there is, together with the ordinary acid salts, free acid present, which is in combination with urea. If, in urines which have an acid reaction, cloudiness does not occur at all on addition of the reagent, they contain only the ordinary acid salts. According to the investigations of O. Hammarsten\* it appears, however, that variations in the amount of the hyposulphite of sodium added can change the results indefinitely, so that its value as a reagent for free acids and acid salts in the urine is somewhat doubtful.

Urine can be kept for a long time in a closed vessel, protected from contact with the air, without undergoing true decomposition. If we allow free access of air, however, it undergoes peculiar, not unimportant decompositions, which we will now consider more closely. If we leave fresh urine alone in an uncovered vessel, we perceive, in most cases very soon, the formation of light, small clouds of mucus, which gradually sink to the bottom, and in which we find with the aid of the microscope a few pavement epithelial cells from the bladder and urethra, as well as a very few mucus corpuscles enclosed in a finely granular coagulum of mucus. We can also frequently readily see the separation of acid urates. On long standing, however, especially at a moderate temperature, the acid reaction frequently becomes stronger and distinct, and usually colored crystals of uric acid are deposited on the walls and bottom of the glass. It remains in this condition of increasing acidity for a few days at least, though it may last for two or even three weeks; finally we notice that the acidity suddenly diminishes until it at last disappears entirely. The urine loses color, becomes lighter, and covered with a whitish iridescent pellicle, and gradually takes on an alkaline reaction, which is shown by an offensive ammoniacal odor. At this time the crystals of uric acid also disappear, and we see white granules and colorless, highly refractive, prismatic crystals of ammonio-magnesian phosphate.

These changes are embraced under the names of the acid and alkaline fermentation of urine.

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\* Jahresbericht für Thierchemie, Band 4, p. 211.



Scherer has furnished interesting explanations of this decomposition; these are essentially as follows. He considers the primary cause of the acid fermentation of urine to be the vesical mucus, which he regards as a ferment necessary to the decomposition of the extractive coloring matter; the latter is decomposed by the mucus with the formation of lactic and acetic acids, so that an increase in the amount of the free acids is brought about. As an indication, and also, probably, as a cause of this act of fermentation, the urine now shows under the microscope considerable numbers of fermentation spores, which in appearance are very similar to those of yeast, only smaller, and which, like the latter, increase by budding, and are grouped together in rows. (Plate II., figs. 1, 2, and 4.) By the formation of these strong acids the readily decomposable urates are broken up with the separation of uric acid, which is then deposited in well-formed crystals. Almost always crystals of calcic oxalate are found in this sediment, concerning the formation of which I will speak more fully under sediments. (Plate II., fig. 4.)

If, after a longer or shorter time, the free acid begins to diminish, then the second period of urinary fermentation, the alkaline, commences. Urea now suffers a decomposition, and becomes converted into carbonate of ammonium;\* gradually the precipitated crystals of uric acid disappear, and whitish granules of urate of ammonium, and prismatic crystals of urate of sodium, which often cover the crystals of uric acid which are commencing to dissolve, appear instead. (Plate II., fig. 5.) As the decomposition increases and the alkaline reaction commences, a part of the ammonia combines with the phosphate of magnesium present in the urine, and very beautiful crystals of ammonio-magnesian phosphate, together with phosphate of calcium, separate in large amounts. (Plate II., figs. 3, 5.) This peculiar decomposition has the closest connection with the formation of sediments, and I shall return to it when I speak of them.

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\* Together with carbonate of ammonium small amounts of other volatile bases, so-called substituted ammonias, appear to form also, of which Dessaignes has already observed trimethylamin, characterized by its odor of sea-fish, by the distillation of large amounts of human urine. (*Annal. der Chemie und Pharm.*, Band 100, p. 128.)

According to Voit and Hofmann\* there is no acid fermentation of urine, but only an alkaline one. The gradual separation of amorphous and crystalline uric acid sediments they explain by the decomposing action which the acid phosphate of sodium exerts on the urate of sodium, whereby the acid reaction of the urine gradually diminishes, so that at no time can an increase in acid be proved. This in many cases is undoubtedly correct, but not in all. As soon as yeast spores occur in a urine, and such cases are not rare, the increase of acid can be readily determined, most easily in very weak saccharine as well as in diabetic urines in which sediments of crystallized uric acid frequently and rapidly form, in spite of the fact that in pronounced cases of diabetes the other constituents of the urine, not excepting the acid phosphate of sodium, are very much diluted. As a product of this fermentation, acetic acid appears, which can be readily separated from every old urine, especially from old diabetic urine, in considerable quantity.

According to the investigations of Schönbein, there is a fungus in every urine which forms gradually and undergoes fermentation, and which in a short time changes pure urea into carbonate of ammonium. According to Pasteur and Tieghem, a torula is present which forms in the interior of the fluid, especially on the bottom of the glass, as a white deposit. Under the microscope this shows rosary-like strings or clumps of small round globules with a diameter of 0.0015 millim., without granulations or recognizable sheath, and which seem to increase by a process of budding.

Of all the substances which occur in human urine, without doubt urea is by far the most important, and as we have already seen above, is essentially the final product of the retrograde metamorphosis of tissue. Urea forms the middle step by which the nitrogen, which has become useless in the body, is given back to inorganic nature, since, when once removed from the body, it decomposes very easily, in contact with decomposing matter, into ammonia and carbonic acid, to begin the circle anew in this form as food for plants. Next to urea comes uric acid, which is also the result of the metamorphosis of the nitrogenous constituents of the body; it stands a step higher than urea,

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\* Zeitschrift für analyt. Chem., Band 7, p. 897.

and decomposes by continuous oxidation into urea and carbonic acid. Its amount is very much less than that of urea, and it is not in a free state like the urea, but is in combination with bases.

Besides uric acid, we meet also in all urine with small amounts of hippuric acid, the origin of which is not yet precisely proved, although it is probable that it is formed in a similar manner to urea and uric acid, and is an intermediate product in the process of retrograde metamorphosis. Besides these bodies, every urine contains, in addition, small amounts of xanthin, kreatinin, oxaluric acid, and coloring and extractive matters, about the chemical nature, origin, etc., of which but very little is yet positively known. Liebreich\* claims to have found in urine a small amount of an organic base which has a resemblance to neurin, obtained by him by the destruction of protagon by baryta water, and which possibly may be a product of the oxidation of the neurin. We also find of mineral constituents, chlorides, chloride of sodium, chloride of potassium, and small amounts of chloride of ammonium, besides phosphates, especially acid phosphate of sodium and small quantities of magnesium and calcium phosphates and sulphates, traces of iron and silicic acid. Schönbein has also detected small quantities of nitrates, which in the alkaline fermentation of the urine are converted into nitrous acid, likewise traces of peroxide of hydrogen. A certain not altogether inconsiderable amount of carbonic acid from the blood, flowing through the urinary organs, gets into the urine and is eliminated with it.

According to Bechamp, all normal urine contains also a peculiar ferment, nephrozymose, which, like the ferment of saliva, is capable of changing starch into sugar. Finally, that constituent of the urine, which, under certain conditions, as I first discovered after the addition of a solution of chloride of zinc, shows a beautiful emerald-green fluorescence, has been recently more carefully investigated by Jaffé,† and since he found the same thing in bile, it has been named urobilin.

Besides the hitherto mentioned organic and inorganic normal constituents of urine, there are the pathological and so-called accidental ones. The former are: albumen, sugar, biliary mat-

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\* Bericht der deutschen chem. Gesellschaft, Band 2, p. 12. Chem. Centralblatt, 1869, p. 12.

† Zeitschrift für analyt. Chem., Band 3, p. 246, und Band 9, p. 150.

ters, fat, mucin, leucin, tyrosin, and several others which are met with in the urine in certain disturbances of the health, while the latter, the accidental, may be of very different sorts, according as one or the other body is accidentally or intentionally introduced into the economy, and is removed with this fluid, either unchanged or after previous chemical decomposition.

We will now consider more particularly the different normal constituents, organic and inorganic, as well as the pathological and accidental ones.

## II. NORMAL CONSTITUENTS OF URINE.

### A. Organic.

#### § 2. UREA.

Formula : $\text{CH}_4\text{N}_2\text{O}$	Carbon	20.00
	Hydrogen	6.67
	Nitrogen	46.67
	Oxygen	26.66
		<hr/> 100.00

A. *Presence.* Urea is found in the urine of mammalia, birds, and reptiles; it is most abundant in that of the carnivora. But, besides in the urine, we find it constantly in the blood, where it often is very considerably increased, especially in kidney diseases (Bright's disease), or after extirpation of the kidneys. This last circumstance indicates that urea is not formed in the kidneys, but in the blood, by an oxidation of nitrogenous matters which have become useless, fragments of tissue or superfluous nitrogenous bodies in the blood.

In the muscular juice of men and sucking beasts, urea has hitherto not been detected, though other bodies have been found, as kreatin, xanthin, sarkin, etc., from which urea can be produced artificially. Whether the above bodies, among which also belongs the uric acid normally found in the blood, are the precursors of urea, and after further decomposition are excreted partly as urea, is not yet perfectly proved; at least it appears from Voit's experiments\* that the kreatin of muscle takes no

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\* Zeitschrift für Biologie, Band 4, p. 77, etc.

part in the formation of urea, and also the experiments of Ssubotin, according to whom urea is formed from kreatin under the influence of the renal tissue, have not been confirmed.\* On the other hand, it is an established fact that, after the introduction of uric acid, guanin, allantoin, thein, gluten, glycocoll, and leucin, also after partaking of food rich in nitrogen, an increase in the urea can readily be determined.†

Moreover, the experiments of von Knieriem‡ showed that chloride of ammonium, asparagin, and asparagic acid increase the urea in urine, a fact which is the more interesting in that asparagic acid has been detected by Radziejewski and E. Salkowski§ among the products of the digestion of fibrine by means of pancreatic ferment.

Besides in the urine, urea is found normally in the blood,|| bile, and liver, in the amniotic fluid, in the vitreous and aqueous humors, and finally, Funke and others have found it in the sweat. Wurtz found it in the lymph and chyle of several animals; Lefort, in the milk of healthy cows. Urea appears to be wanting normally in the muscle of human beings and of most vertebrates. At least it has not been possible, thus far, to detect it in this tissue. It is probable, however, that urea occurs in the muscles and organs of many animals where it has hitherto not been found in mankind. Städeler and Frerichs found considerable quantities of urea in the muscle and in almost all of the organs of many cartilaginous fishes (plagiostomes), while they sought in vain for it in corresponding parts of the body of bony fishes.

If the separation of urea by the kidneys is more or less impeded, or even entirely suspended, we see it appear in almost all of the animal fluids. It first seems to be increased in the blood, and readily passes thence into the serous exudations; under these circumstances urea has been found in the juice of muscle, in saliva, in the vomitus, and even in pus and milk. The sweat is then especially rich in urea, so that after its evaporation a slight crust of urea remains.

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\* R. Gscheidlen's Habilitationsschrift, Leipzig, 1871.

† Bericht der deutsch. chem. Gesellschaft, 1869, p. 566.

‡ Zeitschrift für Biologie, Band 10, p. 268.

§ Berliner Berichte, Band 7, p. 1050.

|| Annal. der Chem. Pharm., Band 156, p. 88.

After the artificial introduction of urea into the body under normal circumstances it is not decomposed, but the economy frees itself very quickly from it, so that we may often, within a few minutes, detect a considerable increase of the urea in the urine. Gallois saw a rabbit weighing two kilograms die, after being given twenty grams of urea. First there occurred an increase of the respiration, then followed weakness of the limbs, trembling, general convulsions, tonic spasms, and finally death.

The urine of a healthy individual contains, on an average, with a mixed diet, 2.5 to 3.2 per cent. of urea, so that within twenty-four hours between 22 and 35 grams are eliminated. The amount of urea excreted, however, is very variable, and depends very much on the weight of the body and on the food. Thus, Lehmann with a purely animal diet saw the twenty-four hours' amount of urea increase to 58 grams; on a diet poor in nitrogen, on the contrary, it fell to less than fifteen grams, but with entire deprivation of food the urea did not ever wholly disappear.

The artificial formation of urea can be brought about in very different ways. For example, cyanate of ammonium, which has the same elementary composition as urea, becomes urea immediately upon heating its solution. It can, moreover, be produced from kreatin, guanin, allantoin, alloxan, oxamide, and many other bodies. Uric acid, by the action of strongly oxidizing substances, produces as final products only urea, carbonic acid, and water. Nathansen obtained urea by heating carbonic ether with an excess of ammonia, and also by the action of chloro-carbonic oxide gas on dry ammonia gas. I can confirm both of these methods of formation. According to Basaroff it is also formed by prolonged heating of dry carbamate of ammonium, and also ordinary sesquicarbonate of ammonium, in sealed tubes, to 130° or 140° C.

#### B. Preparation.

1. *From Urine.* Two volumes of urine are treated with one volume of baryta solution, such as is used for the quantitative estimation of urea, the precipitate of phosphate and sulphate of barium is filtered off, and the filtrate evaporated to dryness on a water bath. The residue is extracted with alcohol, after filtering is again evaporated to dryness, and the mass which now remains is treated with absolute alcohol. The solution

contains pure urea which after evaporation crystallizes in the form of colorless needles. Should the urea thus obtained not be perfectly colorless, it can be made so by treating it with a little pure animal charcoal.

For the isolation at the same time of kreatinin, xanthin, and urea from one and the same specimen of urine, see below under Xanthin, § 5.

2. *From Cyanate of Ammonium.* 80 grams of dried ferrocyanide of potassium are melted by gentle heat with 30 of carbonate of potassium, until a specimen removed solidifies to a milk-white glass. When this point is reached, the crucible is removed from the fire, and 150 grams of red oxide of lead are gradually added in small portions; it is then heated about ten minutes, with frequent stirring, and the mass is poured on to an iron plate. After cooling, the raw cyanate of potassium is dissolved in a solution of 80 grams of sulphate of ammonium in 4 or 500 of water, filtered when all is dissolved, and the filtrate evaporated to dryness. The dried mass is extracted with small portions of alcohol (1–200 grams, 90 per cent.), boiled several times, filtered, the alcohol distilled off again, and the mass allowed to crystallize.

J. Williams recommends using commercial cyanide of potassium instead of the ferrocyanide. He extracts the fused mass oxidized by red oxide of lead with cold water; after powdering it, frees the filtrate from the carbonates by the addition of nitrate of barium, and thus precipitates from the clear solution pure cyanate of lead by the addition of nitrate of lead, and decomposes the former, after washing and drying it, by digesting while hot with the equivalent amount of sulphate of ammonium, dissolved in the necessary amount of water.

C. *Microscopic Properties.* If pure urea is crystallized quickly from a concentrated solution, it appears under the microscope in the form of white, silky, lustrous needles. If, however, we allow the crystallization to take place slowly from dilute solutions, it forms white, almost transparent, beautifully lustrous, striated, four-sided prisms, whose ends are terminated by one or two oblique surfaces. (Funke, Taf. II., fig. 4; 2<sup>o</sup> Aufl. III., 1.) These crystals belong to the rhombic system.

D. *Chemical Properties.* Urea has a bitter, cooling taste, similar to that of saltpetre. Its crystals contain no water of crys-



tallization, are permanent in the air, and readily dissolve in water and alcohol. The solutions are neutral. It is almost insoluble in ether.

1. Urea heated moderately on platinum foil melts with the evolution of ammonia; on being heated somewhat more it solidifies again, becomes brown, and finally burns readily and completely without leaving a residue of carbon.

2. Urea heated with concentrated mineral acids, as sulphuric acid, etc., or with caustic potash or soda, undergoes decomposition. One molecule of water is absorbed, and carbonic anhydride and ammonia are produced. (Quantitative estimation by the method of Ragsky and Heintz.) It undergoes this decomposition also when nitrogenous organic matters capable of decomposition (cause of the alkaline fermentation of urine) are added to its solution; and second, when heated for a long time in a sealed tube with caustic baryta to a higher temperature than 100°. (Quantitative determination by Bunsen's method.)  $\text{CH}_4\text{N}_2\text{O} + \text{H}_2\text{O} = \text{CO}_2 + 2\text{NH}_3$ .

3. If nitrous acid or a solution of mercurous nitrite in nitric acid be added to a solution of urea, it decomposes into water, carbonic anhydride, nitrogen, and ammonia. (Liebig, Wöhler, Ludwig, and Krohmeyer.)  $\text{CH}_4\text{N}_2\text{O} + \text{NH}_4\text{O}_2 + \text{NH}_4\text{O}_3 = \text{CO}_2 + 2\text{N} + \text{NH}_3 + \text{N}_2 + \text{H}_2\text{O}$ . 1 gram of urea furnishes, therefore, 1.2 grams of escaping gas.

According to the investigations of A. Claus,\* the reaction takes place in the above-mentioned way only when the necessary amount of nitrous acid is added to the urea in the cold and then heated; and second, when at the same time with the nitrous acid an equivalent amount of a stronger acid is added. In the last case it is immaterial whether heat is applied at first or later; also the addition of an excess of nitrous acid is not important.

4. If a solution of urea is warmed with nitrate of silver, an insoluble precipitate of cyanate of silver is formed, and the solution contains nitrate of ammonium. In this way it can be converted into the same form of combination (cyanic acid and ammonia), from which it can be produced artificially.

5. Mercuric oxide forms several stable compounds with urea,

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\* Zeitschrift für analyt. Chemie, Band 10, p. 226.



in which, according to circumstances, two, three, or four equivalents of mercuric oxide combine with one equivalent of urea.

6. A solution of mercuric nitrate produces in a solution of urea a white flocculent precipitate, which, according to the concentration of the fluid, has a variable composition. The precipitate contains to one equivalent of nitrate of urea, two, three, or four equivalents of mercuric oxide.

Corrosive sublimate, on the contrary, in a feebly acid solution of urea, gives no precipitate, but it does in an alkaline solution. On this the quantitative estimation of urea and chlorine by Liebig's method depends.

7. Urea treated with a solution of hypobromite or hypochlorite of sodium decomposes into nitrogen, carbonic acid, and water. The carbonic acid is rapidly absorbed by the lye, so that the urea can be determined quantitatively by direct measurement of the nitrogen.\*  $\text{CH}_4\text{N}_2\text{O} + 3\text{NaClO} = 3\text{NaCl} + \text{CO}_2 + 2\text{H}_2\text{O} + 2\text{N}$ . This method, on account of its rapidity, is to be highly recommended for clinical purposes.

8. Urea in alkaline solution at ordinary temperature resists the oxidizing influence of permanganate of potassium very energetically; in a hydrochloric acid solution, however, it decomposes with great readiness on being heated into carbonic acid and ammonia. By this behavior urea appears to be the last end product of the retrograde metamorphosis, since in alkaline solution, as in normal blood, it cannot be further oxidized by oxidizing agents, and is thus essentially distinguished from uric acid, kreatin, guanin, etc., which stand on a somewhat higher step. Urea comports itself quite as indifferently with ozone, while uric acid decomposes very energetically with the production of urea. But in the presence of alkalies urea is decomposed by ozone into carbonic acid and ammonia.†

9. Urea forms with many salts (corrosive sublimate, chloride of sodium, nitrate of calcium, chloride of calcium, etc.) crystallizable compounds; it also forms with many acids, organic (succinic, tartaric, citric, and gallic acids) as well as inorganic, crystallizable salts, of which three, the nitrate, phosphate, and oxalate, are especially important.

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\* Davy, Leconte, Hüfner. *Journ. für prak. Chemie*, 1871, p. 1.

† Compare also Chapman and Smith in the *Chem. Centralblatt*, 1868, No. 308.

a. *Nitrate of Urea.*  $\text{CH}_4\text{N}_2\text{O}, \text{NH}_4\text{O}_3. - (\text{C}_2\text{H}_4\text{N}_2\text{O}_2, \text{NO}_2\text{HO})$ . If tolerably concentrated pure nitric acid, free from nitrous acid, is added to a concentrated solution of urea, this compound separates, after the mixture becomes cool, in white shining plates or scales, which are mostly single, but often in superimposed masses.

If only a small amount of urea is present, the compound is allowed to form under the microscope, best in the following way: The end of a little piece of thread is laid in the drop of fluid to be tested for urea, a covering glass is placed over the drop and one-half of the thread, while the other end of the thread is moistened with a drop of pure nitric acid. The two fluids gradually mingle, and the crystals form under the covering glass on both sides of the thread with great regularity. If the crystals are watched during their formation we find, first, together with many complicated forms, rhombic tables or short prisms, whose acute angle measures  $82^\circ$ . The forms are changed by modification of the obtuse angle by faces into hexagonal tables or six-sided prisms. Such a regular development, however, only occurs during slow crystallization, while, when the crystals form rapidly, a large number of six-sided tables overlap each other like tiles on a roof. Frequently, also, obtuse rhombic octahedra of little durability form at the first meeting of the two fluids, their acute angle measures  $82^\circ$ , but a greater number of particles always accumulate on these, so that the primitive octahedra are changed into the above-named rhombic or hexagonal tables. Finally, very characteristic twin crystals are observed which, with mutually oblique end-surfaces, are formed by the turning of one crystal  $180^\circ$ , corresponding to the well-known forms of gypsum. (Plate II., fig. 6.)

This salt, which is permanent in the air, is readily soluble in water, more difficultly soluble in water containing nitric acid, and most difficultly soluble in alcohol containing nitric acid.

Heated quickly on platinum foil it deflagrates, but at  $140^\circ$  decomposes into carbonic acid, nitrous oxide, urea, and nitrate of ammonium.

On mixing a concentrated solution of nitrate of urea with oxalic acid, the second compound oxalate of urea is precipitated.

b. *Oxalate of Urea.*  $(\text{CH}_4\text{N}_2\text{O})_2, \text{C}_2\text{H}_2\text{O}_4 + \text{H}_2\text{O} - [(\text{C}_2\text{H}_4\text{N}_2\text{O}_2),$

$C_4H_4O_6 + 2HO.$ ] This compound also forms on mixing oxalic acid with a concentrated solution of urea; it is precipitated in long, thin laminæ or in prisms. If the formation is allowed to take place under the microscope, it usually appears similar to that of nitrate of urea in hexagonal tables; at times, however, also in forms of four-sided prisms. (Funke, Taf. II., fig. 6; 2<sup>te</sup> Aufl., III., 3.)

This compound is readily soluble in water, but is precipitated again from the solution by an excess of oxalic acid. On being heated it decomposes into carbonate of ammonium and cyanuric acid.

c. *Phosphate of Urea*,  $C_4H_4N_2O_4 \cdot PH_3O_4$ ,— $[C_4H_4N_2O_4 \cdot 3HO, PO_5]$ , was obtained by Lehmann from the evaporated urine of pigs fed on bran, but it can also be artificially produced in large glistening crystals, belonging to the rhombic system, by phosphoric acid and urea. The crystals are very easily soluble in water, and do not decompose in the air.

E. *Detection*. In order to detect urea in the urine it is sufficient, in most cases, to evaporate a small quantity, 15 to 20 grams, to a syrupy consistence on a water bath, and to treat the residue repeatedly with alcohol until a drop evaporated on a watch glass does not leave any residue. The urea is contained in the alcoholic solution, and remains behind more or less colored after the alcohol is expelled by evaporation on a water bath. Dissolved in a little water, and a part treated with pure nitric acid, and a part with a concentrated solution of oxalic acid, it furnishes the two above-named compounds. If very small quantities are allowed to crystallize with nitric acid under the microscope, the crystalline forms mentioned above, under *nitrate of urea*, will be seen to form. If, however, the urine contains albumen, the above portion is treated with a drop of acetic acid, heated to boiling, so that the albumen is entirely coagulated, filtered, and the filtrate treated as before, first evaporated on the water bath, then the residue extracted with alcohol, etc.

§ 3. KREATININ.

Formula : $C_4H_7N_3O$ [ $C_5H_7N_3O_2$ ]	{	Carbon	42.48
		Hydrogen	6.19
		Nitrogen	37.17
		Oxygen	14.16
			100.00

A. *Presence.* Kreatinin, by all means the strongest base of the animal body, was first discovered by Liebig in the crystalline precipitate which Heintz, and later Pettenkofer, obtained from concentrated urine with a solution of chloride of zinc. Liebig found in this chloride of zinc compound, kreatinin together with kreatin, and therefore arrived at the conclusion that both bodies were originally contained in the urine. But Heintz furnished proof later, by a very thorough investigation, that no kreatin is contained in fresh urine, but that it is formed by the decomposition of the chloride of zinc compound of kreatinin by the absorption of water by the kreatinin, a fact which has now been confirmed by Liebig and Dessaignes. Since kreatin can readily be changed into kreatinin by withdrawing water, the kreatin, which is always to be found in the juice of muscles, becomes in the blood, or, according to Voit, more probably in the kidneys, kreatinin through loss of water, and is then discharged in this form with the urine. Dessaignes, on the contrary, thinks that the fluid of muscle, like the urine, originally contains only kreatinin which first becomes kreatin by the separation of water caused by the long-continued action of warmth in the neutral fluid. But according to my investigations the matter is just the opposite. By the method described under kreatin this body can be obtained pure in a very short time from the juice of muscles; and I have also proved with certainty that kreatin, by long heating in a watery solution, gradually becomes converted into kreatinin. In the juice of muscles there is no kreatinin, but only kreatin, and when the former is found it has been formed from kreatin by the too long action of heat.

According to my own determinations there are from 0.6 to 1.3 grams of kreatinin eliminated by a healthy man on good mixed diet in an average amount of 1,500 to 1,600 cubic centimeters

of urine in the twenty-four hours. Munk found an increased excretion of kreatinin in acute diseases, especially in pneumonia, typhoid fever at the height of the disease, intermittent fever, etc. A diminution occurred during convalescence from acute diseases, especially when the patients were very anæmic.

Hofmann\* found in his extended observations on himself a daily excretion of kreatinin of from 0.52 to 0.81 grm., the average was 0.681 grm.; in others, on the contrary, the average was 0.99 grm. The urine of sucklings was found free from kreatinin; it appeared first after partaking of meat. Boys ten to twelve years old passed a daily average of 0.387 grm.; a person seventy years old, on the contrary, 0.517 to 0.593 grm. In women somewhat less kreatinin, on an average, was found than in men, the average of seven estimations was 0.65 grm. Physical exercise appeared to be without influence; meat diet considerably increased the amount of kreatinin in the urine, even in young children. Hofmann found a diminution of the excretion of kreatinin in cases of debility, deficient nutrition, and in diabetes. In advanced degeneration of the kidneys, in spite of an abundant meat diet, the excretion is diminished, which confirms the opinion of Voit† that the transformation of muscle kreatin does not take place in the blood first, but in the kidneys, where the acid urine is separated from the alkaline blood.

Besides in human urine Verdeil and Marcet found it in the blood, Socoloff in the urine of the horse and sucking calves, Dessaignes in the urine of the cow, and Liebig in the urine of the dog. According to Scherer it appears to be found also in the amniotic fluid. Voit obtained kreatin from the blood of calves, oxen, and sheep, but no kreatinin.

B. *Microscopic Properties.* Kreatinin appears in the form of colorless, very glistening prisms, which belong to the monoclinic system. (Funke, Taf. III., fig. 2; 2<sup>te</sup> Aufl., VI., 5.)

C. *Chemical Properties.* Kreatinin is probably the strongest organic base of the animal kingdom; it has almost as caustic a taste as ammonia, and is soluble in eleven parts of water at 12° to 20°; it is more easily soluble in hot water. One hundred

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\* Virchow's Archiv, Band 48, p. 858.

† Zeitschrift für Biologie, Band 4, p. 114.

parts of cold alcohol dissolve about one part of kreatinin; in hot alcohol it is soluble in such amount, that it separates again on cooling in white crystalline masses; ether takes up only a very small quantity. The solutions have a strongly alkaline reaction and caustic taste, like dilute ammonia.

Kreatinin comports itself like a nitrile base; it directly combines with ethyl iodide, forming kreatinin ethyl iodide, from which ethylkreatinin is separated as a strong base by oxide of silver, and appears in a crystalline form.

1. If a concentrated solution of chloride of zinc is added to a solution of kreatinin, a crystalline precipitate of kreatinin chloride of zinc immediately forms  $(C_4H_7N_3O)_2ZnCl_2 \cdot [C_4H_7N_3O, ZnCl]$ . The crystals are distinctly prismatic when formed very slowly; on more rapid formation, however, only fine needles are seen under the microscope, which, grouped concentrically, either form complete rosettes or tufts, which cross each other, or of which two are so laid together with a short pedicle that they resemble pencils running into each other. Kreatinin chloride of zinc is difficultly soluble in cold water, more readily in hot water, but insoluble in alcohol.

If kreatinin is separated from an aqueous extract of urine by chloride of zinc, the compound is obtained chiefly in the form of dark warty masses, in which, even under the microscope, a crystalline structure can scarcely be recognized. At times even here, distinct crystals in the form of a rosette, fine needles, are obtained, which are united into broom and star-shaped masses. Kreatinin chloride of zinc is obtained from an alcoholic extract of urine by precipitating with an alcoholic solution of chloride of zinc, always as a faint yellow powder, which under the microscope shows almost exclusively yellow, transparent, sharply defined spheres of different size, in which, with a high power (400), a striation may be distinctly seen. By dissolving this powder in hot water, regular forms can readily be obtained under the microscope. When the solution has completely cooled, a drop is placed on an object glass, and a little solution of chloride of zinc is added with the aid of a small piece of thread, just as was described under nitrate of urea, page 17. Very soon the above-described characteristic rosettes of crystals, often of considerable size, are seen to form on both sides of the thread.

2. A not too dilute solution of kreatinin treated with a concentrated solution of nitrate of silver, solidifies to a network of crystalline needles, which dissolve in boiling water, but separate again on cooling.

3. Mercuric chloride acts in a similar way. The precipitate is at first caseous, but changes in a few minutes to a mass of fine colorless needles.

4. A solution of mercuric nitrate does not cause a precipitate immediately in dilute solutions of kreatinin, but if a solution of carbonate of sodium is added to the mixture drop by drop till the turbidity remains permanent, the compound crystallizes in beautiful microscopic crystals. In concentrated solutions the precipitate forms very quickly, and if no free nitric acid is present, without the addition of sodic carbonate.

5. If an ammonium salt is heated with kreatinin, ammonia is evolved.

6. Kreatinin gives with hydrochloric, nitric, and sulphuric acids, good crystallizable compounds, soluble in water:

a. Chloride of kreatinin crystallizes in transparent prisms and broad leaves. With chloride of platinum it gives a compound similar to those formed with potassium and ammonium chlorides, which is easily soluble, and crystallizes in aurora-colored prisms.

b. Sulphate of kreatinin forms concentrically grouped, transparent, quadrilateral tables.

It is to be emphatically remarked that kreatinin chloride of zinc, the most important compound of kreatinin, is not precipitated from chloride of kreatinin, etc., by the addition of a chloride of zinc solution. The separation follows immediately, however, if before the addition of the chloride of zinc solution, acetate of sodium in sufficient amount is added to the kreatinin salt.

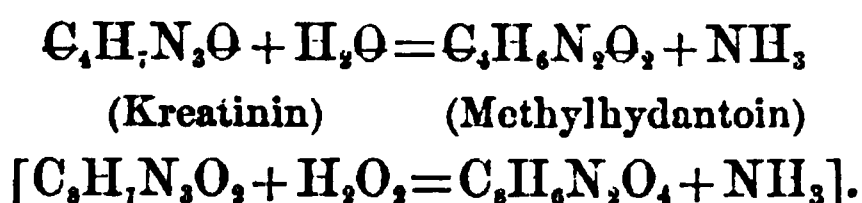
7. By the action of mercuric oxide, lead peroxide, and sulphuric acid, or permanganate of potassium, kreatinin, like kreatin, is decomposed into oxalic acid and oxalate of methyluramin,  $C_4H_7N_3O + O_2 + H_2O = C_2H_7N_3 + C_2H_2O_4 - [C_4H_7N_3O_2 + 4O = C_4H_7N_3 + C_2O_2]$ .

8. Kreatinin is formed from kreatin by the action of the mineral acids, or by the prolonged heating of an aqueous



solution to 100° C., while the latter loses two molecules of water. If a solution of kreatinin is allowed to stand a long time in contact with alkalies, it becomes kreatin again by absorbing water. Warmth favors the transformation. (Liebig, Dessaignes.)

9. On heating with caustic baryta in an aqueous solution, kreatinin furnishes methylhydantoin with disengagement of ammonia. At the same time a syrupy acid is formed which has not been closely examined.



When similarly treated, kreatin forms methylhydantoin together with sarkosin and urea. (See Kreatin.)

Methylhydantoin is formed artificially by melting together sarkosin and urea. (Huppert.)\*

10. Phosphomolybdic acid gives in aqueous solutions of pure kreatinin acidulated with dilute nitric acid a yellow crystalline precipitate, which forms immediately when diluted one thousand times, but only after prolonged standing when diluted from five to ten thousand times. In a great excess of hot nitric acid the compound dissolves, but on cooling it separates in beautiful very characteristic crystals, whose microscopic appearances are not without value in the detection and recognition of kreatinin. (Kerner.)

D. *Preparation of Chloride of Kreatinin from Urine.* Eight to ten liters of urine are evaporated to a third or quarter, and separated after cooling from the precipitated salts. The mother liquor is precipitated with a solution of sugar of lead, the excess of oxide of lead is removed by sulphuretted hydrogen, and a concentrated solution of corrosive sublimate is added to the filtrate, which is nearly neutralized with sodic hydrate. The precipitate, principally a compound of kreatinin with mercuric chloride, is suspended in water and decomposed with sulphuretted hydrogen, the filtrate decolorized with animal charcoal and evaporated to crystallization. By repeated crystallization

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\* Bericht. der deutschen chem. Gesellschaft, Band 6, p. 1278.



from strong alcohol, white crystalline crusts are finally obtained, or large, hard, shining prisms of chloride of kreatinin. The removal of hydrochloric acid is accomplished by plumbic hydrate, as is shown below. (Maly.)

*E. Detection.* Since kreatinin occurs only in small amount in the urine, large quantities are necessary for its certain recognition, yet 2 to 300 cubic centimeters are sufficient for its qualitative detection in most cases. The process is as follows: The fresh urine is neutralized with milk of lime and the phosphoric acid precipitated by a solution of chloride of calcium. The precipitate is filtered off, and the filtrate evaporated rapidly on a water bath to a thick syrup. The residue thus obtained is extracted with strong alcohol, best with absolute alcohol, allowed to stand a few hours, filtered, and the clear fluid treated with a concentrated solution of chloride of zinc free from acid. After violent agitation a turbidity will soon appear, and after forty-eight hours the separation of the kreatinin chloride of zinc is complete. The compound is washed on a filter with alcohol, dried, and, according to C. 1, subjected to a microscopic examination. If we wish to produce pure kreatinin, the compound which has been obtained is dissolved in a little hot water, and oxide of zinc and hydrochloric acid separated by freshly precipitated thoroughly washed plumbic hydrate, with which the fluid is to be boiled at least a quarter of an hour. The fluid obtained by filtration is decolorized by boiling with animal charcoal, and is then evaporated to dryness. The residue, which is always a mixture of kreatinin and kreatin, is treated with cold strong alcohol, by which the kreatinin is removed while the kreatin remains behind. By evaporation of the alcoholic solution kreatinin is obtained in pure crystals, while the kreatin is obtained readily in pure form by recrystallization from a little hot water of the residue insoluble in alcohol. It is to be observed that, when the solution of kreatinin chloride of zinc has been treated for a long time with oxide of lead, often only kreatin and no kreatinin at all is found in the residue. The latter becomes converted into kreatin by the prolonged action of the excess of oxide of lead by absorbing two molecules of water.

If the urine contains albumen, it must first be separated by coagulation. In diabetic urine it is best, according to Gaeht-

gens,\* to first destroy the sugar present by fermentation with yeast.

Kreatinin thus obtained is characterized by its strong basic qualities, by its tendency to form double compounds with the metallic salts, and salts with acids, as well as by its characteristic behavior with phosphomolybdic acid. It is distinguished from kreatin further by its much greater solubility in strong alcohol, as well as by its form of crystallization.

Kreatin is not so well characterized; there is nothing better for its certain recognition than a comparison with the pure crystalline substance.

The alcoholic extract of urine, from which, after acidifying with hydrochloric acid, hippuric acid has been separated by shaking with ether, § 8, E. 2, is best used for the detection of kreatinin. After the ether is removed, the hydrochloric acid is accurately neutralized with sodium hydrate, diluted with thirty to forty cubic centimeters of absolute alcohol, and the kreatinin precipitated by the chloride of zinc solution.

According to Kerner, kreatinin may easily be detected by the following method: The urine is precipitated with a concentrated solution of mercurous nitrate, filtered, treated with sulphuretted hydrogen which is separated from the filtrate by warming and the addition of a drop of nitric acid, and while it is still warm is treated with phosphomolybdic acid. After cooling and standing a short time the phosphomolybdate of kreatinin separates in characteristic crystals, especially on the walls of the vessel, where they have been rubbed with a glass rod. (See above under C. 10.)

#### § 4. KREATIN.

<b>Formula :</b> $C_4H_7N_3O_3 + H_2O$ $[C_4H_7N_3O_4 + 2HO]$	{	<b>Carbon</b>	<b>36.64</b>
		<b>Hydrogen</b>	<b>6.87</b>
		<b>Nitrogen</b>	<b>32.06</b>
		<b>Oxygen</b>	<b>24.43</b>
		<hr/>	
		<b>(Anhydrous.)</b>	<b>100.00</b>

A. *Presence.* Kreatin is found in the juice of striated, and also of smooth muscular fibre, according to my investigations,

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\* Zeitschrift für analyt. Chem., Band 8, p. 100.

on an average of 0.2 per cent. It has, moreover, been found in greater or less quantity in the various transudations, in the blood, the brain, the kidneys, and the amniotic fluid. (See remarks under kreatinin concerning its presence in the urine.)

Not much can be said definitely about the physiological significance of kreatin. If we regard only its occurrence in the juice of muscle as well as its considerable richness in nitrogen, we would be inclined to regard kreatin as an important nutritive material; but the ready decomposition of this body into urea, kreatinin, and sarkosin, which are without doubt to be regarded as excretive materials, stamp it rather as an excretive material, which stands on the ladder of retrograde metamorphosis as a middle step between those substances of the most complex (protein substances) and those of the simplest molecular composition (urea, etc.). At all events, kreatin stands nearer to urea than to the protein substances.

*B. Preparation.* Fresh, finely-chopped beef is thoroughly mixed with an equal amount of water, and the mass heated ten or fifteen minutes on a water bath with constant stirring to  $55^{\circ}$ – $60^{\circ}$  C., so that the albumen just commences to coagulate. It should then be strained through cloth, the residue squeezed out, and the fluid thus obtained heated to boiling to completely coagulate the albumen. After cooling it is filtered, and the filtrate treated with basic acetate of lead in slight excess. The lead precipitate is collected on a filter, washed, and the excess of lead precipitated from the entire filtrate by sulphuretted hydrogen. After filtration from the sulphide of lead, a colorless filtrate is obtained, from which, after sufficient concentration on the water bath, colorless kreatin crystallizes out after standing awhile. The crystals are to be collected on a filter, washed with alcohol, and dried in the air. After one recrystallization they are obtained absolutely pure.

Kreatin may be obtained artificially, by warming an alcoholic solution of sarkosin and freshly prepared cyanamid for several hours to  $100^{\circ}$  C. on the water bath.\*

For its preparation from urine, see kreatinin under "Detection."

*C. Microscopic Properties.* Kreatin, when pure, forms colorless,

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\* Volhard, Chem. Centralblatt, 1869, p. 864.

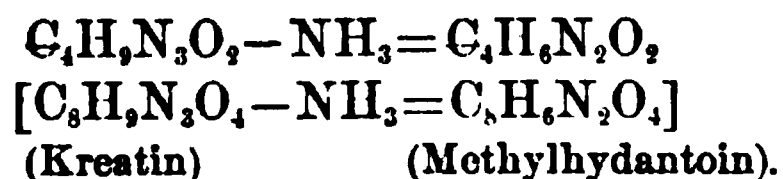
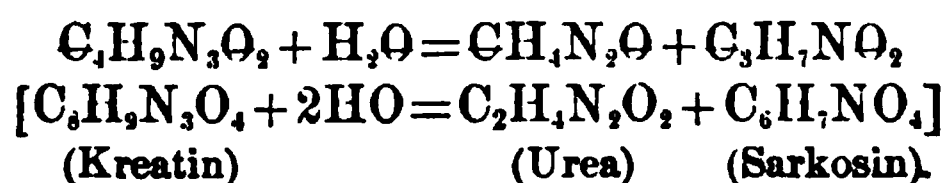
perfectly transparent, strongly refractive prisms which belong to the monoclinic system. (Funke, Taf. III., fig. 1; 2<sup>te</sup> Aufl., Taf. IV., fig. 4.) In most cases it forms groups whose appearance reminds one of that of sugar of lead.

If a dilute solution of kreatin is placed in a concave polished object glass and allowed to evaporate spontaneously, at first on the edge, a collection of long prismatic crystals is observed which are thick at their free ends and gradually become narrower. In the middle of the fluid regular crystals gradually form, principally prisms, which are often united by their acute angles in a fan shape. Single crystals have, in the middle, a characteristic bulging like those of lactate of zinc, narrowing toward the ends, and are terminated by two surfaces. Finally, also, thick, apparently rectangular, tables, at times single, at times in large numbers, frequently appear.

*D. Chemical Properties.* Kreatin has a bitter, harsh taste, dissolves in seventy-five parts of cold water, and much more readily in hot water; the kreatin separates from the solution again on cooling, as crystals, in the form of fine shining needles. It is with difficulty soluble in alcohol, one part requiring nine thousand four hundred and ten parts; while ether does not dissolve any.

1. The aqueous solution is without reaction on vegetable coloring matters, has a bitter taste, and very readily decomposes. If a dilute solution of kreatin is evaporated slowly on the water bath, it gradually becomes converted into kreatinin. Dessaignes has recently succeeded in producing crystallizable salts of kreatin with sulphuric, hydrochloric, and nitric acids.

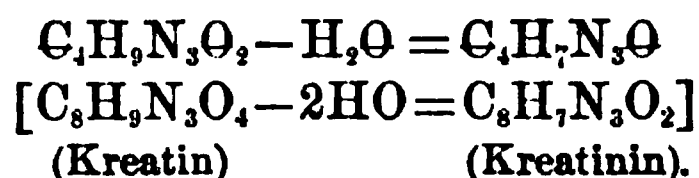
2. If kreatin is boiled a long time with caustic baryta it decomposes into urea, sarkosin, and methylhydantoin.



If the action continues too long, the urea splits up into carbonic acid and ammonia; the latter escapes while the carbonic acid combines with the barium. Sarkosin can be obtained in

colorless crystals, though with difficulty; methylhydantoin crystallizes more easily, and can be separated from the sulphate of sarkosin by treating with alcohol.

3. Dilute mineral acids dissolve kreatin without decomposition, but boiled with concentrated acids it changes into kreatinin by giving up water.



4. Pure kreatin in dilute solution is not precipitated by chloride of zinc. From a concentrated solution kreatin chloride of zinc crystallizes in hard crystals. Similar compounds are furnished by kreatin with chloride of cadmium, chloride of copper, and mercuric nitrate.

5. Peroxide of lead has no action on kreatin; it is, on the contrary, decomposed by permanganate of potassium; the decomposition products which are formed, with the exception of carbonic acid, are unknown. Perhaps urea is one of them.

6. A solution of kreatin, boiled with an excess of mercuric oxide, causes metallic mercury to be separated with evolution of carbonic anhydride, and the solution contains the oxalate of another powerful base, methyluramin ( $\text{C}_2\text{H}_7\text{N}_3$ ). (See § 3, C. 7.)

E. *Detection.* See Kreatinin.

## § 5. XANTHIN.

<b>Formula :</b> $\text{C}_5\text{H}_4\text{N}_4\text{O}_2$ $[\text{C}_{10}\text{H}_4\text{N}_4\text{O}_4]$	$\left\{ \begin{array}{l} \text{Carbon} \\ \text{Hydrogen} \\ \text{Nitrogen} \\ \text{Oxygen} \end{array} \right.$	39.5
		2.6
		36.8
		21.1
		<hr/> 100.0

A. *Presence.* Xanthin was recognized by Scherer and Städeler as a substance very widely distributed in the animal economy, while, until within a short time, it was known only as a very rare constituent of some vesical calculi. Scherer found xanthin in human urine, in the spleen, pancreas, brain, liver of the ox, in the thymus gland of the calf, and in the muscular tissue of the horse, ox, and fish, also in the spleen in cases of splenic tumor,

as well as in the liver in acute yellow atrophy. Mosler\* found xanthin in the blood and urine in leukæmia. Dürr and Stromeier found it in the urine after the use of sulphur baths. Bence Jones observed it once in a ten-year-old child as a urinary sediment. Xanthin was mostly accompanied by hypoxanthin; but in the spleen, liver, and brain by uric acid also. Salkowsky† proved the presence together with xanthin of a hypoxanthin-like body in very small amount in normal as well as in leukæmic urine.

**B. Microscopic Properties.** Xanthin is amorphous, and shows under the microscope no crystalline structure. A hot aqueous solution of xanthin deposits it on cooling, mostly in the form of colorless flocculi, at times, also, as a fine powder, which under the microscope appears to consist of round bodies which, when in the flocculent form, are arranged in rows, and in the powdered lie singly.

**C. Chemical Properties.** Xanthin forms hard, white pieces, which on rubbing with the nail assume a waxy lustre. It is difficultly soluble in cold water, and somewhat more soluble in boiling water. It has been produced artificially from guanin.

1. Ammonic and potassic hydrates, hydrochloric, nitric, and sulphuric acids dissolve xanthin. It is precipitated from its alkaline solutions by the addition of an acid, while it gives crystalline compounds with the acids.

2. The cold saturated aqueous solution gives with corrosive sublimate a white precipitate; when diluted thirty thousand times an evident cloudiness occurs, but when diluted forty thousand times it is not perceptible; with cupric acetate yellowish-green flocculi separate on boiling. The solution in ammonia is precipitated by chloride of cadmium and chloride of zinc, also by plumbic acetate; the latter precipitate often changes, on standing, into shining scales.

3. Nitrate of silver causes in a nitric acid solution of xanthin a flocculent precipitate, which dissolves on heating and slowly separates again on cooling. Under the microscope the silver compound shows after rapid cooling hairlike, crystalline needles, but on slow cooling wavy aggregations of fine crystals are formed.

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\* Mosler declares he found sarkin (hypoxanthin), but the reactions described by him correspond rather to those of xanthin than sarkin.

† Virchow's Archiv, Band 50.

In an ammoniacal solution of xanthin, nitrate of silver gives a gelatinous precipitate insoluble in ammonia.  $\text{C}_5\text{H}_4\text{N}_4\text{O}_3 + \text{Ag}_3\text{O} \rightarrow [\text{C}_{10}\text{H}_4\text{N}_4\text{O}_4 + 2\text{AgO}]$ .

4. Xanthin dissolves in nitric acid on heating without evolution of gas, and a yellow residue remains after evaporating the solution, which residue does not become purple by the action of ammonia, but becomes yellowish red by adding potassic hydrate, and when heated beautiful violet red.

If uric acid is mixed with xanthin, as is the case in certain calculi which contain it, the above reaction is modified by the murexid reaction which takes place at the same time. This is the reason, according to Lebon,\* why xanthin has been so seldom found in calculi. To separate the two the powdered calculus is to be treated with hydrochloric acid and heated. Since uric acid is insoluble in hydrochloric acid, the filtrate contains only chloride of xanthin, which can be obtained by evaporation and used for the above reaction.

5. If xanthin is dissolved in strong hot hydrochloric acid, beautiful microscopic crystals of chloride of xanthin separate on slow cooling in the form of six-sided tables, lying together in groups and rosettes. Very frequently, however, only spherical and oval forms can be seen. The nitric acid salt crystallizes in a similar form though not so characteristic; here also rosettes are seen to form from rhombic tables and prisms.

6. If calcic hypochlorite is mixed in a watch glass with sodic hydrate, and a little xanthin added, a dark green border first forms around the granule and soon becomes brown and finally disappears. (Hoppe-Seyler.)

7. Phosphomolybdic acid produces, even in very dilute solutions of xanthin, a copious yellow precipitate. In hot dilute nitric acid this compound is soluble, but it separates, after cooling again, in regular microscopic cubes. (Scherer, Kerner.)

8. Xanthin occupies the middle step between sarkin (hypoxanthin) and uric acid.

Sarkin	$\text{C}_5\text{H}_4\text{N}_4\text{O}$	$[\text{C}_{10}\text{H}_4\text{N}_4\text{O}_2]$
Xanthin	$\text{C}_5\text{H}_4\text{N}_4\text{O}_2$	$[\text{C}_{10}\text{H}_4\text{N}_4\text{O}_4]$
Uric acid	$\text{C}_5\text{H}_4\text{N}_4\text{O}_3$	$[\text{C}_{10}\text{H}_4\text{N}_4\text{O}_6]$

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\* Comptes rendus, Bd. 73, p. 47.



D. *Detection.* I give below a method which not only insurès the detection of xanthin in urine, but also at the same time enables us to obtain kreatinin and considerable amounts of chemically pure urea in one and the same portion of urine.

1. *Xanthin.* Fresh urine is treated with a mixture of baryta water and nitrate of barium in a decanting jar, till all of the phosphates and sulphates are precipitated. When the precipitate has thoroughly settled, the clear fluid is removed with a siphon, and evaporated in a large porcelain dish over a gas stove. The latter not only renders water baths for this sort of work superfluous, but also allows of a much quicker evaporation without ever bringing the fluid to boiling. The syrupy mother liquor, from about fifty liters of urine, is poured off from the salts crystallized out after cooling, diluted to four or five liters, treated with about a pound of ammonia, and precipitated with an ammoniacal solution of nitrate of silver. As soon as the precipitate is settled, the supernatant fluid is removed with a siphon, the silver compound is collected on a filter and washed with distilled water until the filtrate no longer reacts with chlorine. When this point is reached, the filter is laid on blotting paper and kept there until the moist precipitate can be readily removed, it is then put into a flask and dissolved by boiling in as little nitric acid of a specific gravity of 1.1 as possible. In most cases a complete solution follows, and only a few flocculi of chloride of silver remain behind; the heat is continued till the fluid, at first very dark colored, has become light yellow. Soon yellow flakes of nitrate of xanthin silver oxide separate from the filtrate. Since, however, the silver compound of xanthin separates from the nitric acid solution much more slowly than the corresponding sarkin compound, the fluid is allowed to stand at least eight to twelve days; from the first a too great excess of nitric acid should be avoided. The nitrate of xanthin silver oxide is collected on a filter, washed and digested, for the removal of nitric acid, with ammonio-nitrate of silver. After washing again, the yellow-colored silver compound is suspended in water, and, after the addition of a little hydrochloric acid, heated to boiling and decomposed by sulphuretted hydrogen. The filtrate which is still colored yellow is decolorized completely by treating it with some well-extracted animal charcoal, and after concentration the chloride



of xanthin separates in small hard crystals. By repeatedly evaporating the chloride of xanthin with ammonia, and finally washing out the chloride of ammonium with cold water, pure xanthin is obtained. The amount obtained is very small—with less than one or two hundred pounds of urine the work should not be undertaken. The nitric acid solution, from which the nitrate of xanthin silver oxide was crystallized, contains the rest of the xanthin compound, and, as I believe, other silver compounds also. On the addition of ammonia, a considerable amount of gelatinous, yellow precipitate falls, with which a considerable amount of the silver xanthin compound is always mixed.

2. *Kreatinin*. The ammoniacal mother liquor, from which the xanthin was precipitated by nitrate of silver, is heated again on the gas stove, when the ammonia escapes, and the excess of silver added separates at the same time. If the fluid no longer smells of ammonia it is filtered, and the clear fluid evaporated to a syrup. After cooling, about an equal volume of alcohol is added, it is allowed to stand twenty-four hours, decanted from the nearly crystallized salts, and mixed with a concentrated neutral alcoholic solution of chloride of zinc, when, after a short time, very pure, faintly yellow kreatinin chloride of zinc precipitates, which is used for obtaining kreatin and kreatinin by the familiar method with freshly precipitated hydrated oxide of lead, etc.

3. *Urea*. The alcoholic mother liquor, from which kreatinin was precipitated, is mixed with an equal volume of pure nitric acid of specific gravity 1.2, and allowed to stand in the cold twenty-four hours to crystallize out the nitrate of urea. The crystalline mass is placed on porous tiles, allowed to dry, dissolved in water and boiled with pure animal charcoal. The filtrate remains yellow, and after evaporation deposits large amounts of yellow nitrate of urea. All of the products of crystallization are dissolved in water, and the boiling solution treated with small amounts of permanganate of potassium until it has become absolutely colorless. After evaporation the nitrate of urea crystallizes out perfectly colorless. To obtain pure urea, the nitrate is finally decomposed by freshly precipitated carbonate of barium, evaporated, most of the nitrate of barium allowed to crystallize out, the mother liquor brought to complete dry-

ness, and the urea extracted, while cold, with five times its amount of alcohol (93 per cent.). After distilling off the alcohol, the urea separates in masses of pure crystals.

## APPENDIX.

### *Hypoxanthin (Sarkin).*

Hypoxanthin, or sarkin,  $C_5H_4N_4O$  [ $C_{10}H_4N_4O_2$ ], which is of constant occurrence in the juice of muscle, has hitherto not been found in the urine with certainty, although Salkowsky succeeded in separating a body from normal as well as leukæmic urine, which corresponded with sarkin in its characteristics, except in a few particulars. Sarkin was certainly detected in the medulla of bone from leukæmic persons by Salkowsky, and also in fifteen pounds of normal calves' bones. The method above described by me for separating xanthin, serves for detecting the sarkin, the nitrate of silver compound of which differs from the corresponding xanthin one only by its being very much less soluble in nitric acid. The masses which separate immediately on cooling from the boiling nitric acid solution of the silver compound, will have some sarkin present. To separate it with certainty it is recrystallized, after the addition of one cubic centimeter of the nitrate of silver solution, once or twice from hot nitric acid, and that portion which first separates is collected on a filter, washed, and digested for a time with an ammoniacal silver solution to remove the nitric acid, filtered, washed, the precipitate suspended in water, heated to boiling, and decomposed with sulphuretted hydrogen. The colorless filtrate leaves, after evaporation, pure crystallized sarkin.

Sarkin is distinguished from xanthin, especially in the following particulars:

1. The nitrate of sarkin silver oxide completely separates from hot nitric acid immediately on cooling. The compound shows, under the microscope, long colorless needles, which do not blacken on exposure to light. The corresponding xanthin compound separates, after a long time, in scaly masses.\*

2. Pure sarkin, after careful evaporation with nitric acid,

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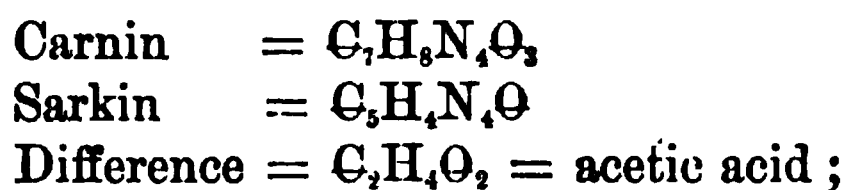
\* Zeitschrift für analyt. Chemie, Band 6, p. 83.

does not furnish a deep-yellow residue, but an almost colorless, or, at most, a light-yellow one, which, on the addition of hydrate of sodium, becomes somewhat darker, but not, as in the case of xanthin and guanin, red yellow.

3. Sarkin does not give, with hydrate of sodium and calcic hypochlorite, a green color.

4. Sarkin separates from hot water in a crystalline form xanthin, on the other hand, amorphous. (See § 5, B.)

Weidel found a new base in Liebig's meat extract, carnin,  $C_7H_8N_4O_3 + H_2O$ , which yields, on heating with nitric acid, nitrate of sarkin, together with some oxalic acid. Carnin contains, therefore, the elements of sarkin and of acetic acid :



but on account of its stability when treated with baryta water, it is not to be regarded as acetate of sarkin.

If carnin or sarkin is heated with fresh chlorine water and a trace of nitric acid until the slight evolution of gas has ceased, then evaporated to dryness on a water bath, and the white residue exposed under a receiver to ammonia vapor, in a short time a dark rose-red color appears.

The formula of carnin differs from that of theobromin only in possessing one atom more of oxygen.

F. Baumstark\* found first in the urine of a dog fed on benzoic acid, then in icteric, and finally, also in normal human urine, a new crystalline body by the following procedure :

The urine, carefully concentrated to a syrup on the water bath, or over a gas stove, is, while it is still warm, mixed with large quantities of alcohol, the spirit is distilled off from the filtered alcoholic solution, the hippuric acid removed from the residue after acidifying with hydrochloric acid by shaking with ether, and the fluid thus freed after supersaturation with ammonia, completely precipitated with basic acetate of lead. The fluid filtered from the lead precipitate is freed from surplus lead by sulphuretted hydrogen, and evaporated to a syrup.

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\* Bericht. der deutsch. chem. Gesellschaft, Band 6, p. 883. Annal. der Chemie, Band 178, p. 392.

The new body, together with urea, separates from this residue after long standing, and remains insoluble on treating the crystalline mass with alcohol. The new hitherto nameless body crystallizes out of hot water in white prisms, similar to those of hippuric acid, which melt at over  $250^{\circ}$  C. Heated on platinum foil, thick white fumes are evolved with dissemination of a peculiar odor. Heated in a small tube, the body yields an inflammable gas, which smells like ethylamin and blues litmus. The crystals dissolve with tolerable readiness in hot water, with difficulty in cold water and alcohol. They are insoluble in absolute alcohol and ether.

Analysis gave the formula  $C_5H_4N_4O_3$  ( $C_6H_5N_4O_3$ ). It forms readily soluble salts with acids, but no compounds with bases. The solution is precipitated by mercuric nitrate. Lactic and paralactic acids form on treating it with nitrous acid; boiling it with baryta water evolves at first one-half of the nitrogen in the form of ammonia; and afterwards the rest as ethylamin with separation of carbonate of barium.

### §. 6. URIC ACID.

Formula : $C_5H_4N_4O_3$ [ $C_{10}H_8N_8O_6$ ]	{	Carbon	35.72
		Hydrogen	2.38
		Nitrogen	33.33
		Oxygen	28.57
			100.00

**A. Presence.** Uric acid is found in the urine of all classes of animals, and occurs even in the very lowest orders. The excrement of birds (guano), snails, reptiles, and insects is rich in uric acid. Besides in the urine, it was detected also in normal blood of hens, by Meissner, and after extirpation of the kidneys by Strahl and Lieberkühn\* and recently by Garrod.† According to the latter, it appears constantly increased in the blood in gout. It has further been found in the spleen, lung tissue, muscular juice of the heart, the pancreas, brain, and liver, and finally in gouty deposits. R. Bender‡ found on the surfaces

\* Strahl and Lieberkühn. Harnsäure im Blute, etc., Berlin, 1848.

† Prager Vierteljahresschrift, Band 5, S. 4, Abth. II., p. 12.

‡ Journ. für prac. Chemie, 1866, III., p. 254.

of the face, stomach, and liver of a body exhumed after two months' burial, small white spots, which consisted of uric acid crystals.

The amount of uric acid in human urine is less dependent on the food taken, as is the case with urea, than on special internal conditions of the economy. Under normal conditions, according to Becquerel, 0.495 to 0.557 grams of uric acid are eliminated by a healthy man in twenty-four hours. According to my own experiments, instituted on a powerful healthy young man of twenty-three years of age, there was an average secretion of 36.4 grams of urea and 0.827 grams of uric acid in 2,000 cc. of urine in twenty-four hours. Further observations have shown me, however, that in the normal condition the amount of uric acid may vary considerably, and may fluctuate within twenty-four hours between 0.2 and 1 gram. According to Ranke, the proportion of uric acid to urea varies from 1:50 to 1:80 in twenty-four hours. An increase of uric acid results, first of all, from disturbed digestion, as well as generally insufficient nutrition. Moreover, it is found to be increased in all febrile conditions, and especially in affections of the respiratory organs and disturbances of the circulation. In a case of leukæmia Salkowsky \* found, during a series of observations extending over thirty days, that the uric acid was permanently increased, not alone in percentage, but also absolutely, especially in relation to the urea. An average of thirty estimations gave a proportion of uric acid to urea of 1:16.3, which is more than a threefold increase.

If uric acid is taken into the body it is decomposed normally into carbonic acid and urea, but yields also oxalic acid, whenever the process of oxidation has undergone a retardation in any way.

B. *Preparation*.—1. *From Human Urine*. Freshly filtered morning urine is treated with hydrochloric acid (20 cc. to 1 liter of urine), and allowed to stand forty-eight hours. The uric acid will be found separated in more or less deeply colored crystals, which are specially adapted for microscopic study.

2. *From Excrement of Serpents*. The excreta of serpents are boiled with a solution of one part of potassic hydrate in twenty

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\* Virchow's Archiv, Band 50.

parts of water until the ammoniacal odor has disappeared. Carbonic anhydride is conducted into the filtered solution until it is nearly neutral, and the acid urate of potassium, which is thus separated, is collected and washed with water. After washing, the potassium salt is dissolved in potassic hydrate, and the solution filtered into dilute hydrochloric acid, care being taken that the latter is always present in excess; the precipitate is pure uric acid, which, after washing and drying, is obtained as a delicate light powder.

C. *Microscopic Properties.* Uric acid appears in many different forms under the microscope, chiefly, however, as smooth tables of rhombic form. These are sometimes colored, are always of extraordinary transparency, and vary in size—often being by no means small. The tables are frequently modified, so that spindle-shaped crystals are formed by the rounding off of the obtuse angles, with which are mixed short barrel-shaped cylinders. Frequently, however, six-sided plates, rectangular tables, or rectangular four-sided prisms with abrupt terminations appear; these often lie collected together in peculiar rosettes. Besides these, other modifications occur, as saw-shaped, fan-shaped, or tooth-shaped crystals. (Plate I., figs. 2 and 3; Plate II., fig. 4; Plate III., fig. 1.)

I succeeded in obtaining very manifold forms of uric acid, whose character could readily be seen by comparison with Funke's plates, by treating a normal urine with different amounts of hydrochloric acid. If the nature of any crystal is doubtful, however, it is very easy to bring it into the usual form; it is dissolved on an object glass in a small amount of potassic hydrate, and a drop of hydrochloric acid is added, when the usual tabular and spindle forms are seen to occur.

D. *Chemical Properties.* Pure uric acid prepared from the excrement of serpents forms white, very light, delicate-feeling crystalline scales, which, seen under the microscope, show the above-described forms. It is without taste and odor, is very difficultly soluble in water (one part of uric acid requires fourteen to fifteen thousand parts of cold water, and eighteen to nineteen parts of hot water), the solutions obtained do not red-den litmus. In dilute hydrochloric acid it is quite as insoluble, and is not at all soluble in alcohol and ether. It is readily soluble in concentrated sulphuric acid without decomposition,

but is precipitated from this solution again by diluting with water.

1. It is quite readily soluble in a solution of phosphate of sodium as well as in that of many other salts of the alkalies. It takes from these salts a part of the base, with which it combines, and thus gives rise to the formation of acid salts. It is contained in the urine in this form, together with the acid phosphate of sodium, which is the chief source of the acid reaction of urine. It is easy to obtain a fluid similar to urine, with an acid reaction, by dissolving uric acid in a warm solution of phosphate of sodium, and from this fluid crystals of urate of sodium are deposited on sufficient concentration. (For the separation of the latter from the urine, see Sediments.)

If the acid solution, which results from dissolving uric acid in phosphate of sodium, is allowed to stand a long time at a temperature of 20° to 30° C., after a few days bacteria form, the acid reaction diminishes, and the fluid gradually becomes alkaline. After eight to fourteen days all of the uric acid is decomposed, and the fluid contains urea and carbonate of ammonium. Other products, as allantoin, oxalic acid, etc., do not appear to be formed in this decomposition. (Lex.)

2. If uric acid is heated in a glass tube it is decomposed, without, however, previously melting. It breaks up into urea, cyanuric acid which forms a sublimate, hydrocyanic acid, and a little carbonate of ammonium, which can be recognized by its odor. In addition peculiar oily products are observed, and a porous carbon containing nitrogen is left behind.

3. If uric acid, made into a pulp with water, is boiled with peroxide of lead, it decomposes into four bodies: carbonic anhydride, allantoin, urea, and oxalic acid. The allantoin which is naturally present in the urine of calves, as well as the urea, can be easily obtained by crystallization and recognized, the oxalic acid remains in combination with the lead, while the carbonic anhydride escapes with effervescence. According to Pelouze a little allanturic acid is formed also. It is not improbable that the urea which occurs in this decomposition is a further product of the oxidation of allantoin, and the carbonic acid a product of the oxidation of oxalic acid, so that the simplest decomposition of uric acid by peroxide of lead is into allantoin ( $C_4H_6N_4O_3$ ) [ $C_5H_8N_4O_4$ ] and oxalic acid.



4. If hydriodic or hydrochloric acid is allowed to act on uric acid in sealed tubes at  $160^{\circ}$  to  $170^{\circ}$  C., it decomposes into glycocoll, carbonic anhydride, and ammonia. (Strecker.) On prolonged heating of uric acid with double its weight of concentrated sulphuric acid, in addition to glycocoll, a body similar to xanthin (pseudoxanthin) and hydurilic acid result. (O. Schultzen and Filehne.)

By this formation of glycocoll from uric acid, a close chemical relationship between uric acid and hippuric acid, the characteristic constituents of the urine of carnivora and herbivora, is foreshadowed.\*

5. Permanganate of potassium and ozone act very energetically on uric acid; allantoin, carbonic anhydride, oxalic acid, and urea are formed, or by ozone in an alkaline solution, urea, ammonia, oxalic acid, and carbonic anhydride.

6. If one part of uric acid is gradually added to four parts of concentrated nitric acid (specific gravity = 1.420), it is dissolved with effervescence, and finally the whole fluid solidifies to a crystalline pulp. The uric acid at the same time decomposes into alloxan ( $C_4H_2N_2O_4$ ) [ $C_8H_2N_2O_8$ ] and urea; the first separates in the form of crystals, the latter by the simultaneous formation of nitrous acid decomposes immediately into carbonic acid and nitrogen, which escape and cause the effervescence of the fluid.

7. If reducing agents, such as, for example, sulphuretted hydrogen, hydrogen gas, etc., are allowed to act on the solution of alloxan, very soon crystals of a new body, alloxantin, separate ( $C_8H_{10}N_4O_{10}$ ) [ $C_{16}H_{10}N_4O_{20}$ ]. This body is much more difficult to dissolve than alloxan, it crystallizes in oblique four-sided prisms, and becomes red when exposed to ammonia vapor.

Alloxan and alloxantin give rise to the most important uric acid reaction. If a solution of alloxan and alloxantin is treated with ammonia, it becomes purple red, and after standing a time crystals of murexid are deposited. These form four-sided prisms, which reflect light of a cantharides-green color; triturated they form a brown powder, and dissolve in water with a deep purple color. It always serves for the detection of uric acid.

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\* *Annal. der Chemie und Pharm.*, Band 146, p. 142. *Chem. Centralblatt*, 1868, p. 490.



8. Uric acid treated with moderately dilute nitric acid dissolves, and alloxantin is found as the chief product of the reaction. If we carefully evaporate this solution almost to dryness, alloxan is formed from a part of the alloxantin by the further action of nitric acid. If now ammonia is allowed to act on the mixture, the beautiful color of murexid is produced. This color of murexid is rendered purple blue, by caustic potassa. By means of this reaction the smallest amounts of uric acid are readily detected. If the residue is treated immediately with potassic or sodic hydrate, instead of with ammonia, a magnificent purple-violet solution is obtained, which, however, becomes paler on heating, and finally, before the fluid is entirely evaporated, loses its beautiful color completely. (Distinction from xanthin, see Xanthin.)

According to Hardy, modified red alloxan forms first on evaporating uric acid with nitric acid, and on the addition of ammonia it is changed into red isoalloxanate of ammonium.

9. Uric acid forms salts with the bases which are more or less readily soluble in water; the most soluble is the lithium salt. Crystalline uric acid is separated from these solutions on the addition of hydrochloric acid, acetic acid, etc. In concentrated solutions the separation takes place immediately; in dilute, as for example urine, only after long standing, as twenty-four or thirty-six hours. The crystals are readily recognized under the microscope. For the different salts, see Sediments.

10. An alkaline solution of uric acid reduces nitrate of silver immediately, even in the cold. If a trace of uric acid is dissolved in a solution of sodic carbonate, and a paper on which a drop of nitrate of silver solution has been allowed to spread is wet with it, a dark spot immediately forms, even when the uric acid is diluted one-thousand-times, but still smaller quantities, even to one five-hundred-thousandth of a gram, after a few seconds show a distinct yellow reaction without its being necessary to heat. (Schiff.)

11. If a solution of uric acid in potassic hydrate is added to an alkaline copper solution, a white precipitate of cupreous urate is formed. If the latter is heated to boiling with an excess of the solution of copper, the uric acid oxidizes, and red cupreous oxide separates, while the products of the oxidation of uric acid, allantoin, urea, and oxalic acid, remain in solution.

12. If a bromidized alkaline solution of hypochlorite of sodium is allowed to act on uric acid, an intense rose-red fluid is formed. The color disappears after a time, especially if more of the bromine solution is added. (Dietrich.)\*

E. *Detection.* It is to be noticed here that urine which is undergoing acid fermentation frequently deposits uric acid in more or less deeply colored crystals. In diabetic urine, especially, one finds not infrequently after a short time all of the uric acid as a red, sandy, crystalline powder on the bottom of the glass.

1. 100 to 200 cc. of urine are evaporated in a porcelain evaporating dish on a water bath. If the urine contains albumen, it must first be coagulated by boiling after the addition of a drop of acetic acid, filtered, and the filtrate evaporated to a syrupy consistency. By frequently treating with alcohol the urea is extracted from the residue together with the extractive matters and the salts soluble in alcohol; the uric acid, on the other hand, remains behind with the insoluble salts and mucus. The salts are removed by pouring over it a small amount of dilute hydrochloric acid, and uric acid is obtained alone with a small amount of mucus. The following tests are to be employed to insure its perfect recognition:

a. A few drops of nitric acid are poured over a small portion in a watch glass. The specimen dissolves more or less completely on warming, and after evaporating on a water bath leaves a reddish residue behind. If this residue is moistened with dilute ammonia (one part to ten of water), the purple-red murexid appears instantly, which, by addition of a drop of potassic hydrate, becomes purple blue. If the amount of uric acid present is very small, an excess of ammonia can very easily hinder the reaction, therefore it is safer to bring a glass rod moistened with ammonia near it, and to allow the ammonia vapor to blow over the residue. The test thus performed will react certainly and beautifully with mere traces of uric acid.

b. The remainder is dissolved in a few drops of potassic hydrate, in which the mucus will remain undissolved. From this solution of urate of potassium the uric acid is precipitated

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\* Zeitschrift für analyt. Chem., Band 4, p. 176.

in a crystalline form by the addition of hydrochloric acid, and is recognized under the microscope.

2. The following method is simpler: About 200 cc. of urine are treated in a beaker with 5 cc. of hydrochloric acid, and allowed to stand twenty-four to forty-eight hours. At the end of this time the uric acid will be found separated in the form of colored crystals, which partly float on the surface, and partly are deposited on the sides and bottom of the glass. An examination, under the microscope, as well as a test of the filtered crystals, with nitric acid and ammonia, will permit its easy recognition as uric acid.

3. If there is only a small amount of fluid to test for uric acid, it is to be poured on a shallow watch glass, and with from four to eight grams, six to twelve drops of strong acetic acid are to be added, and after a thread about an inch long is laid in the fluid, it is to be allowed to stand eighteen or twenty-four hours, at a temperature at most of 16° to 20° C. At the end of this time the uric acid will have separated in crystals on the thread, which must, therefore, be examined microscopically. This method is particularly fitted to test the blood-serum of gouty patients for uric acid. (Garrod.)

### § 7. OXALURIC ACID.

Formula : $C_8H_4N_2O_4$ [ $C_6H_4N_2O_8$ ]	{	Carbon	27.27
		Hydrogen	3.03
		Nitrogen	21.21
		Oxygen	48.49
			<hr/>
			100.00

A. *Presence.* Schunk\* first proved the occurrence of oxaluric acid, combined with ammonia, in normal urine. This discovery renders it more than probable that other members also of the large series of uric acid derivatives occur in normal or pathological urine, whereby additional information in reference to physiology and pathology may be obtained.

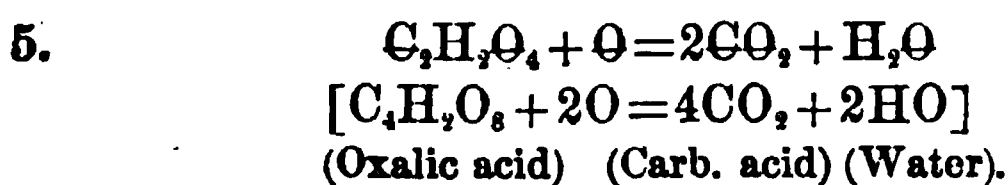
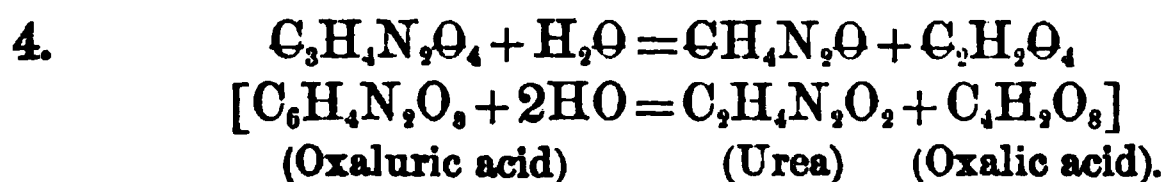
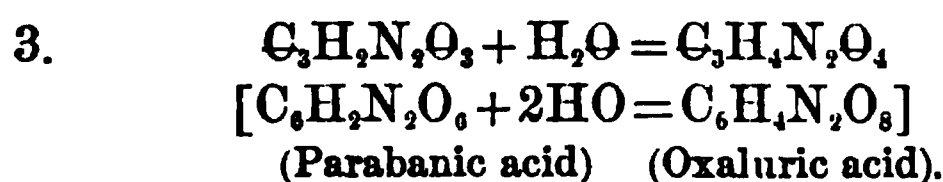
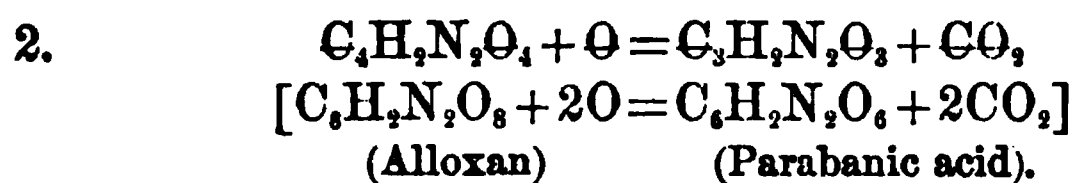
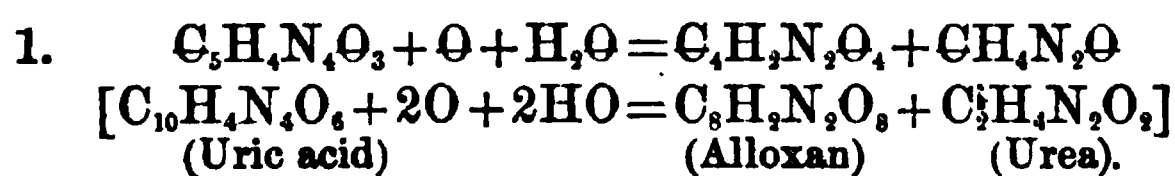
Oxaluric acid stands in close relation to uric acid, xanthin,

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\* Proceed. of the Royal Society, vol. 16, p. 140. Zeitschrift für analyt. Chem., Band 6, p. 499, and Band 7, p. 225.

and guanin, and also to urea. Uric acid, treated with nitric acid, yields first urea and alloxan; the latter by further oxidation gives, with the development of carbonic acid, parabanic acid, which is also obtained by treating guanin and xanthin with chlorate of potassium and hydrochloric acid. Parabanic acid becomes oxaluric acid by absorbing water, and this, on boiling with water, splits up into urea and oxalic acid.

The following equations show the gradual decomposition of uric acid into urea, oxaluric acid, carbonic acid, and water :



**B. Preparation.** A solution of uric acid in warm very dilute nitric acid, when treated with ammonia, immediately after cooling, yields, on evaporation, crystals of oxalurate of ammonium. The same salt is obtained by boiling parabanic acid with ammonia, and evaporating the solution. Hydrochloric acid separates the oxaluric acid from a concentrated solution of oxalurate of ammonium, as a light, white, crystalline powder.

**C. Microscopic Properties.** If a drop of a solution of pure oxalurate of ammonium is evaporated on an object glass under the microscope, long prisms, with pointed ends, are seen, which unite to form beautiful double tufts, or more or less complete rosettes. If the salt is not perfectly pure, the tufts of needles remain small, and form spherical aggregations which

are studded on the periphery with fine, prominent, crystalline needles. If a drop of nitric acid is brought in contact with such crystalline aggregations, the rosettes of prismatic crystals change, while still maintaining their opposed position, into a warty clump of oxaluric acid crystals.

If a solution of oxalurate of ammonium is treated with nitric acid, a white crystalline powder separates according to the concentration, either immediately or after long standing, consisting chiefly of indistinctly defined oxaluric acid crystals. After short or long standing in the nitric acid fluid, sometimes only after several days, the separated oxaluric acid disappears again, and a drop of this solution now allowed to evaporate on an object glass readily shows the characteristic forms of nitrate of urea under the microscope.

D. *Chemical Properties.* Free oxaluric acid is a white, crystalline powder having an acid taste, very difficultly soluble in water. The oxalurate of the alkalies, like that of ammonium, is soluble in water; the other salts, on the other hand, are difficultly soluble or insoluble.

1. An aqueous, tolerably dilute solution of oxalurate of ammonium, treated with chloride of calcium and ammonium, does not give rise to a precipitate; the fluid remains perfectly clear. If the mixture is then warmed, there occurs very soon, far before the boiling point, a cloudiness, and calcic oxalate separates in large quantities. This reaction gives, doubtless, the most delicate test, and with it incredibly small amounts of oxaluric acid can be detected with the aid of the microscope. If the solution was too concentrated, the precipitated calcic oxalate will be amorphous. Dilute solutions, however, especially when the fluid contains coloring matters, etc. (as, for example, a dilute solution of oxalurate of ammonium in urine), give, when treated in this way, a precipitate of calcic oxalate, insoluble in acetic acid, and showing under the microscope the most beautiful quadrilateral octahedra. If the microscopic examination should show no well-formed crystals of calcic oxalate, it is easy to bring the amorphous into the crystalline form. For this purpose the precipitate is allowed to settle, the fluid is decanted from it, and it is dissolved in one to two drops of hydrochloric acid. If then the hydrochloric acid solution is tolerably diluted, and carefully covered with a layer of ammonic hydrate, on quiet

standing, the two fluids gradually mix, and as soon as the calcic oxalate has completely separated again, the microscope will show a greater or less number of the most beautiful quadrilateral octahedra. With care this reaction never fails, and with the very characteristic form of the calcic oxalate it is most delicate and decisive.

2. If a solution of oxalurate of ammonium is boiled with hydrochloric acid, in a few minutes oxalic acid can be detected by adding ammonia and chloride of calcium.

3. An aqueous solution of oxalurate of ammonium, with nitrate of silver, does not give a precipitate immediately; after a few minutes, however, fine crystalline needles separate, which on sufficient concentration at last fill the whole fluid, and under the microscope appear as very fine hair-like needles, arranged in stars and rosettes. The silver salt does not blacken on exposure to the light, and readily dissolves in ammonia. The ammoniacal solution does not become reduced by boiling.

4. A tolerably concentrated solution of pure oxalurate of ammonium does not give a precipitate immediately when treated with sugar of lead solution. After a few minutes the mixture becomes cloudy, and oxalurate of lead separates as a heavy crystalline powder, which appears under high powers of the microscope, as very well formed four-sided prisms, with six end surfaces. If the oxalurate of ammonium is not quite pure, its aqueous, tolerably concentrated solution is treated with the lead salt, the precipitate which takes place immediately is filtered off, and the filtrate is left at rest, when the characteristic crystals will soon separate. According to my experience the lead salt in the crystalline form is more easily obtained from impure material than the silver salt.

5. The addition of chloride of calcium or chloride of zinc to moderately concentrated solutions of oxalurate of ammonium causes crystalline deposits of the salts of these metals to separate after long standing; these also show very characteristic forms under the microscope.

*E. Detection.* The urine is filtered through animal charcoal to separate the oxalurate of ammonium. This salt is retained by the charcoal, and can be withdrawn by boiling it with alcohol. I use the apparatus shown in the accompanying figure, which,

in fact, allows several hundred liters of urine to be used with little oversight. The apparatus (fig. 1) is intelligible without

FIG. 1.

a description; the pipette, A, of about 400 cc. capacity, is filled with finely granulated animal charcoal, such as is used in sugar manufactories. The screw of the stop-cock, C, is regulated so that the urine runs off in drops, and during twenty-four hours sixteen or twenty liters pass through the charcoal. If the decolorizing power of the charcoal, covered with a new piece of fine linen from time to time to catch the epithelium, etc., ceases, the pipette is emptied and filled with new charcoal, so that the filtration can be continued for weeks.

The charcoal saturated with coloring matters, etc., is next washed with distilled water, until the filtrate no longer reacts for chlorine and phosphoric

acid; it is then dried in the air, and finally is repeatedly boiled with alcohol until the latter is no longer colored yellow. Washing and boiling require some patience, yet may be successfully performed. The greater part of the alcohol is next distilled off from the golden-yellow alcoholic solution, the rest of the fluid is evaporated in a porcelain dish on a water bath, either in the open air or under a hood with a good draught, since a fearful urinous odor, which persistently sticks to the clothing, is evolved by it, such as I do not ever remember to have experienced in so great a degree in all my many labors with urine. On treating the residue with lukewarm water, a tenacious fatty mass remains be-

hind, in which Schunk has found a crystalline fatty acid. The aqueous brown solution, however, yields after evaporation a syrupy residue, from which, after long standing in the cold, crystalline oxalurate of ammonium separates. To shorten this process I have made use of dialysis through parchment with the best results. Even if the separation is not absolutely complete, the sufficiently concentrated diffusate soon solidifies to a crystalline mass. The rest of the syrupy mother liquor is extracted with absolute alcohol, the crystalline residue is washed with alcohol a few times and then dissolved in hot water, the solution obtained is digested with a very small amount of purified animal charcoal, filtered, and the colorless filtrate evaporated, when on sufficient concentration pure oxalurate of ammonium separates. The yield is only very small, yet I obtained from 100 to 150 liters of urine, according to the method described, a sufficient amount to recognize this interesting body by all of its characteristic qualities, and to compare it with the pure salt prepared from parabanic acid.

### § 8. HIPPURIC ACID.

Formula : $C_9H_7NO_3$ $[C_{15}H_9NO_6]$	Carbon	60.34
	Hydrogen	5.03
	Nitrogen	7.82
	Oxygen	26.81
		<hr/>
		100.00

**A. Presence.** Hippuric acid is present chiefly in the urine of herbivora. It is found in human urine in normal as well as in abnormal conditions. Bence Jones found in the twenty-four hours' urine of a small man 0.32 gm. of hippuric acid and 0.5 gm. of uric acid; in a heavy man, 0.42 gm. of hippuric acid, and 0.82 gm. of uric acid. Before meals the urine of both persons always contained less hippuric acid and also less uric acid in one thousand parts of urine than after meals. Thudicum found on the average in the urine of an adult in twenty-four hours 0.169 to 0.315 gm., and even as much as 1.0 of hippuric acid. After taking plums the twenty-four hours' amount increased to 2.212 gm. Hallwachs obtained from the twenty-



four hours' amount of urine of different persons, even in a preponderance of meat diet, nearly 1.0 grm. of hippuric acid.

Hippuric acid is found to be increased by a purely vegetable diet, especially after taking plums, red whortleberries, mulberries, asparagus, and further, after the internal use of benzoic acid, oil of bitter almonds, toluol, cinnamic acid, kinic acid, etc. Succinic acid, on the contrary, causes no increase of hippuric acid, according to Hallwachs, but according to Meissner is eliminated with the urine unchanged. In several diseases, especially in high fevers and in diabetes, an increased secretion of hippuric acid appears to occur. Besides in the urine, hippuric acid has been detected in small amount in the suprarenal capsules of the ox, in diseased human blood, and also in ichthyosis scales. The source of hippuric acid in the urine may be twofold; first, bodies may be ingested with the food which are converted into hippuric acid in the economy. Hallwachs was unable to find benzoic acid in the ordinary grass fodder of the cow, but Zwenger and Siebert found in bilberry bushes tolerable quantities of kinic acid, as did also Schwarz and Oehren in different sorts of galium; we know that kinic acid is changed into hippuric acid in the economy. If kinic acid is wide-spread in the vegetable kingdom, which can scarcely be doubted, the great richness of the urine of herbivora in hippuric acid is thereby very simply explained. But in the oxidation of albumen in alkaline solution with permanganate of potassium, considerable amounts of benzoic acid appear, wherefore it is more than probable that at least a part of the hippuric acid discharged with the urine is also formed by the metamorphosis of nitrogenous constituents of the body.\*

According to the investigations of Meissner and Joly,† the urine of rabbits, after being fed on meadow hay and clover, contains much hippuric acid as well as urea. The former almost entirely disappears from the urine, however, after exclusive feeding with carrots (*Daucus carota*), and is immediately replaced by succinic acid to such an extent that benzoic acid does not appear. Meissner and Joly arrive at the conclusion

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\* Meissner and Shepard, Untersuchungen über das Entstehen der Hippursäure, Hannover bei Hahn, 1866. J. Erdmann, Chem. Centralblatt, 1866, p. 897.

† Zeitschrift für Chem., Neue Folge, Band I., p. 230. Chem. Centralblatt, 1866, p. 239.

that the formation of hippuric acid, and what appears to be the chief thing, of benzoic acid, is directly dependent on the character of the food, and is not a characteristic of metamorphosis in the herbivorous organism independent of the character of the food. According to the investigations of Wildt, feeding on *Leontodon taraxacum* (dandelion) causes a not inconsiderable increase of hippuric acid in the urine.

B. *Microscopic Properties.* If a hot saturated solution of hippuric acid is allowed to cool rapidly, the crystals under the microscope appear in the form of fine needles and hairs. It separates in regular, well-formed crystals, however, from a dilute cold saturated solution. It forms in this way, milk-white, semi-transparent, four-sided prisms and pillars, which are terminated by two or four surfaces. The typical form is always a vertical rhomboid prism. (Plate I, fig. 1.) Single crystals at times resemble those of ammonio-magnesian phosphate, from which, however, hippuric acid is easily distinguishable by its chemical behavior.

C. *Preparation.* Fresh horse or cow urine (5 to 6 liters) is boiled with an excess of milk of lime a few minutes, then filtered, the clear solution of hippurate of calcium is quickly evaporated to an eighth or a tenth of its original volume, and treated with hydrochloric acid. After twenty-four hours the hippuric acid is crystallized out, is dissolved again with milk of lime to purify it, and is allowed to crystallize again from the filtrate after the addition of hydrochloric acid. If it is not colorless even then, it can be treated in aqueous solution with well-burned animal charcoal. After the filtrate cools, it then separates in the form of colorless, transparent, long crystals. The mother liquor yields after evaporation a second crystallization.

Loewe treats the fresh urine with sulphate of zinc, evaporates it together with the precipitate which takes place to one sixth, filters rapidly, and separates the hippuric acid from the filtrate by hydrochloric acid; it is then to be recrystallized to purify it. This method gives a very pure preparation.

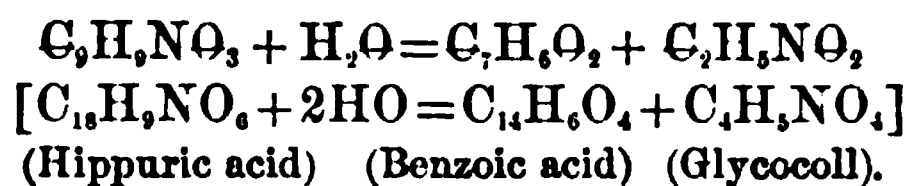
An efficient procedure to purify colored hippuric acid is given by Güssmann. The crystals are dissolved in a sufficient amount of dilute sodic hydrate, and a solution of permanganate of potassium is added, drop by drop, to the fluid heated to boil-

ing, until a portion filtered off gives a white precipitate with hydrochloric acid. The entire filtrate, while still hot, is treated with a slight excess of hydrochloric acid and allowed to crystallize.

D. *Chemical Properties*.—1. Hippuric acid is odorless and has a slightly bitter taste. It requires six hundred parts of cold water to dissolve it, but much less hot water. Alcohol takes it up readily, ether with more difficulty but yet completely. The solutions redden litmus strongly.

2. Hippuric acid heated in a small glass tube melts to an oily liquid. If it is allowed to cool it solidifies to a milk-white crystalline mass. On being heated more strongly it decomposes, benzoic acid and benzoate of ammonium sublime, and at the same time is observed the formation of oily red drops, which diffuse a peculiar odor similar to that of fresh hay; after cooling they harden and are soluble in alcohol and ammonia, but not in water. If the heat is increased to nearly a red heat, an intense odor, like that of hydrocyanic acid, is developed, and a porous charcoal remains behind. This property is very characteristic of hippuric acid, whereby we can recognize it readily and distinguish it from uric acid and benzoic acid, with the latter of which it has very much resemblance. If in this dry distillation the heat is not raised above 250° the hippuric acid yields only benzoic acid colored pale red by some foreign substance, traces of hydrocyanic acid and a liquid body, nitrobenzol, which has the greatest resemblance in odor to oil of bitter almonds.

3. If dilute mineral acids are allowed to act on hippuric acid it is not changed, but is, however, on heating with concentrated hydrochloric, sulphuric, or nitric acids. With these it undergoes a peculiar decomposition; we find that crystalline benzoic acid has separated after cooling, and there remains dissolved in the fluid, combined with the mineral acid, a body which, when free, has a feebly acid reaction, glycocoll,  $C_2H_5NO_2$ ,  $[C_4H_5NO_4]$ .



4. In contact with fermenting or putrefying substances hippuric acid becomes converted into benzoic acid, therefore it often

happens that it is no longer possible to separate it from old urine; the benzoic acid formed volatilizes readily with the steam as soon as a little hydrochloric acid is added to the urine in evaporating it.

5. If nitrous acid is allowed to act on hippuric acid, or nitric oxide gas is conducted into a solution of hippuric acid in nitric acid, it becomes, with the evolution of nitrogen, converted into an acid free from nitrogen, benzoglycolic acid,  $C_6H_5O_4$  [ $C_{10}H_8O_8$ ]. The same decomposition occurs when hippuric acid is dissolved in an excess of dilute potassic hydrate, and the solution is treated in the cold with chlorine gas until no more nitrogen is evolved.

6. Hippuric acid forms crystallizable salts with bases, and can be separated from solutions of its salts after sufficient concentration by hydrochloric acid in the form of long needles.

7. If boiling concentrated nitric acid is allowed to act on hippuric acid, the solution evaporated to dryness, and the residue introduced into a small glass tube and heated, an intense odor of nitrobenzol, similar to that of bitter almonds, is developed. Benzoic acid gives the same reaction. With cinnamic acid the peculiar cinnamon odor conceals every other. Since even mere traces of nitrobenzol diffuse for a tolerably long time a powerful odor, this reaction is applicable to the detection of even very small amounts of hippuric acid. (Lücke.)

Albumen, gluten, uric acid, grape sugar, salicin, salicyluric acid, choloidic acid, anisic acid, pyrogallie acid, kinic acid, picric acid, naphthalin, phtalic acid, indigo, and isatin do not give this reaction.

E. *Detection*.—1. 800 to 1,000 cc. of urine are evaporated on a water bath almost to dryness, the residue is rubbed up with powdered baric sulphate, acidulated with hydrochloric acid, and extracted completely with alcohol. After neutralizing the alcoholic extract with sodic hydrate, the greatest part of the alcohol is distilled off, and the syrupy fluid which remains is, after the addition of oxalic acid, evaporated to dryness on the water bath with constant stirring. The dried mass is then sufficiently exhausted with large amounts of ether, to which some alcohol has been added, and the ethereal solution is distilled almost to dryness. The crystalline residue is then treated, while hot, with milk of lime to remove the oxalic acid, filtered, the

filtrate evaporated to a very small volume, and then feebly acidulated with hydrochloric acid. After some time the hippuric acid crystallizes out. The crystals are to be tested chemically and microscopically. Very small amounts of hippuric acid are detected by the nitrobenzol reaction. (Chemical Properties, 7.)

If, however, the urine is rich in hippuric acid, for example after taking benzoic acid, it is possible to obtain crystals of hippuric acid from it after evaporation to a syrupy consistence, by treating it with a little hydrochloric acid; these crystals are easily separated from the uric acid, which is deposited at the same time, by means of hot water.

2. The following method of Meissner gives an easy and sure means of finding hippuric acid, and at the same time detecting any succinic acid present. 1,000 to 1,200 cc. of urine are precipitated carefully with strong baryta water, the excess of baryta water is removed by a few drops of sulphuric acid, of which an excess is to be avoided, and then filtered. The filtrate, accurately neutralized with hydrochloric acid, is then evaporated on a water bath to the consistency of a thick syrup, and the neutral residue, while still hot, is added to 150 or 200 cc. of absolute alcohol in a closed glass vessel. Any succinic acid salts are precipitated together with the chloride of sodium, etc., while the hippuric acid salts remain in solution. After repeated agitation, as soon as the precipitate has settled well the alcoholic solution is decanted, and the alcohol completely driven off on the water bath, the syrupy residue, which on cooling solidifies to a crystalline mass, is put into a closed vessel while it is still hot, acidulated with hydrochloric acid, and the hippuric acid extracted by shaking with not too small amounts of ether (100 or 150 cc.). After the ether is distilled off, the residue is diluted with water, and heated to boiling with a little milk of lime. The hippuric acid separates from the concentrated filtrate, after the addition of hydrochloric acid, in beautiful crystalline rosettes; they can be obtained entirely free from color by treating with pure animal charcoal.

*Succinic Acid.* Since, according to the investigations of Meissner and Shepard,\* succinic acid also occurs in normal urine,

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\* Meissner and Shepard, Untersuchungen über das Entstehen der Hippursäure, etc., Hannover, 1866.

regard must be paid to it in the qualitative analysis of urine.\* Meissner and Shepard found succinic acid normally in the urine and in the blood: they found it in the urine, sweat, and saliva, after taking benzoic acid, and increased in the blood after the absorption of kinic acid. Succinic acid taken internally, however, causes no increased secretion of hippuric acid, but in not too small doses is eliminated unchanged in the urine.

Since, according to Pasteur's and my own numerous investigations, wine and other fermented drinks contain not inconsiderable quantities of succinic acid, and the latter, at least in part, goes over into the urine unchanged, we have a really frequent source for the occurrence of this acid in normal urine.

Meissner and Joly † found considerable succinic acid in the urine, with exclusive meat and fatty diet; a diminution, and even disappearance of it with vegetable diet, and generally with insufficient nourishment. Succinic acid is formed in the economy also by the reduction of malic acid. It occurs in rabbits after feeding on carrots (*Daucus carota*), also after the exhibition of malate of calcium. Malate of sodium, however, yields only very little succinate, but becomes, for the most part, converted into the carbonate.

Hilger and Koch found large amounts of succinic acid, together with ammonia, after taking asparagus. There is no doubt that succinic acid and ammonia are formed from the asparagin of the asparagus, which does not go over into the urine unchanged, but undergoes the same decomposition in the economy as in the hands of the chemist.

The saline mass precipitated from concentrated urine by absolute alcohol serves for its detection (see above, 2). After this has been thoroughly washed with alcohol, and finally pressed, it is dissolved in as little hot water as possible, hydrochloric acid is added, and the succinic acid present is extracted by shaking with ether (100 to 150 cc.). After distilling off the ether a brown mass remains, from which succinic acid crystallizes out with difficulty. I have found that treatment with nitric acid, by which the succinic acid is not attacked, is sufficient to

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\* Salkowski, from his own numerous investigations, cannot acknowledge the occurrence of succinic acid in human urine as proved. *Archiv der Physiologie*, Band 4, p. 95.

† Loc. cit.



purify it. For this purpose, the ethereal extract is diluted with water, heated to boiling, and treated, while boiling, with pure nitric acid, drop by drop, until the fluid has a barely perceptible yellow color. The succinic acid readily crystallizes from this solution, after concentration. The crystals are placed on blotting-paper, the mother liquor is absorbed, and the slightly yellow acid is used for the following reactions:

1. A portion is sublimed in a small test tube. Succinic acid sublimes at  $120^{\circ}$  to  $130^{\circ}$ .

2. The remainder is dissolved in a little water, and the solution obtained divided into two parts. One part is added to a mixture of alcohol, chloride of barium, and ammonia, when a white deposit of succinate of barium results. The second half is heated to boiling with an excess of carbonate of magnesium, filtered, and treated with a few drops of a neutral solution of ferric chloride, whereupon a voluminous brown precipitate of succinate of iron results. If the succinate of iron is decomposed, after washing, by heating with ammonia, the neutral filtrate gives, with a solution of nitrate of silver, a precipitate of succinate of silver. The silver salt is decomposed by sulphuretted hydrogen, and succinic acid is allowed to crystallize from the filtrate. (Funke, 2<sup>e</sup> Aufl., Taf. II., fig. 5.)

3. Its behavior with the acetate of lead is very characteristic. The precipitate which first takes place dissolves readily and completely in an excess of the reagent, but it separates again on warming and shaking as a heavy crystalline powder.

I succeeded by this method in detecting very small quantities of succinic acid, after it had been added to 800 or 1,000 cc. of normal urine.

Salkowsky prefers to extract the succinic acid with ether. For this purpose the urine is precipitated with baryta, the excess of baryta is removed by sulphuric acid and evaporated. The concentrated solution is then strongly acidulated with sulphuric acid and shaken several times with ether. It is purified as above.

4. Schultzen proposed with good result the following procedure for detecting hippuric acid in icteric urine. The urine is precipitated with acetate of lead, and the filtrate treated with sulphuretted hydrogen and then evaporated. The residue is extracted with alcohol, the extract evaporated, and the hippuric

acid removed from the residue, after addition of hydrochloric acid, by shaking with ether. After evaporating the ether it is taken up with water, shaken with animal charcoal, and the filtrate concentrated on the water bath, when quite pure crystals of hippuric acid separate. If this is not the case, the residue is dissolved in water, and a drop of basic acetate of lead solution added, whereby all of the extractive matters and any benzoic acid present are removed. The filtrate is freed from lead, evaporated, and after cooling treated with hydrochloric acid which separates the hippuric acid. Without the previous precipitation with sugar of lead, often only benzoic acid is obtained from icteric urine.

### § 9. PHENOL.

(Carbolic acid, Phenylic acid, Phenylic alcohol.)

Formula : $C_6H_6O$ [ $C_{12}H_8O_2$ ]	{	Carbon	76.93
		Hydrogen	6.40
		Oxygen	16.67
		<hr/>	
			100.00

A. *Presence.* Phenol was detected by Wöhler in the castor, and was later found by Städeler, together with taurylic, damolic and damaluric acids as a constant constituent of the urine of the cow, human being, and horse. Only a very small quantity of this acid can be separated from human urine, and it is somewhat doubtful whether this poisonous acid exists preformed in the urine, or is first formed during its isolation. According to recent investigations of Buliginisky \* carbolic acid is in fact a product of the decomposition of a yet unknown constituent of the urine, which is soluble in alcohol, and is not precipitated by the acetate or basic acetate of lead and ammonia, but yields carbolic acid by the action of dilute mineral acids.

After the external as well as internal use of carbolic acid, according to Almén,† E. Salkowski,‡ and others, it appears in the urine which frequently assumes an olive-green, deep dark-brown, or even black color, and in the same way, according to

\* Hoppe-Seyler, Med. Chem. Mittheilung., Heft 2, p. 234.

† Neues Jahrbuch d. Pharm., Band 34, p. 111.

‡ Pflüger's Archiv, Band 5, p. 335.



the investigations of Schultzen and Naunyn,\* benzole changes into carbolic acid in the economy and appears as such in the urine.

*B. Chemical Properties.* In a completely anhydrous state phenylic acid crystallizes in long colorless needles, which melt at  $37.5^{\circ}$  C. and boil at  $183^{\circ}$  C. The acid smells like smoke, acts as a caustic, and is poisonous. It is difficultly soluble in water, easily soluble in alcohol and ether. The solution coagulates albumen, and has a strong antiseptic action.

1. Nitric acid allowed to act on phenylic acid, forms first nitro-, then binitro-, and at last trinitro-phenylic acid, which is known under the common name of picric acid or Welter's bitter, and can be produced from indigo, salicin, etc., by treating with nitric acid.

2. Ferric salts occasion in a solution of phenylic acid a violet color, playing into blue, which after a time changes to a dirty white turbidity.

3. Nitrate of silver, and also mercuric oxide, are reduced by phenylic acid.

4. A pine splinter, soaked in an aqueous solution of phenylic acid, and then dipped for an instant into dilute hydrochloric acid, becomes colored deep blue in a few moments after exposure to the rays of the sun. The color obstinately resists the action of chlorine; it becomes lighter to be sure, but returns again when the splinter is dipped in dilute hydrochloric acid.

5. An aqueous solution of phenylic acid, treated with ammonia and calcic hypochlorite, becomes, on heating, a beautiful blue color. (R. Lex.)

To the fluid to be tested a quarter of its volume of ammoniac hydrate is added, then a few drops of the calcic hypochlorite solution (one part of calcic hypochlorite to twenty parts of water), and the mixture is warmed a little, but not to boiling. If the phenol is in large quantity the blue color appears immediately; if its quantity is small a few minutes to a quarter of an hour are required.

Too high a temperature, and also too much calcic hypochlorite interferes with the reaction; great care must be taken, therefore, in regard to the latter point. (Salkowski.)

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\* Reichert's und Du Bois-Reymond's Archiv, 1867, Heft 8.

6. A solution of phenol, heated to boiling with a solution of mercurous nitrate which contains a trace of nitrous acid, gives an intense red mixture, and in concentrated solutions there is a rapid separation of metallic mercury. The reaction is still very distinct when diluted one part in sixty thousand. (Plugge.)

7. A dilute aqueous solution of phenol, treated with an excess of bromine water, gives rise immediately to a yellowish-white flocculent precipitate of tribrom-phenol. On sufficient addition of bromine water the precipitate disappears at first. The washed precipitate, treated in a test tube with a little sodium amalgam and water, and warmed, evolves, if the fluid is treated in a watch glass with dilute sulphuric acid, the characteristic odor of free phenol. This reaction is very delicate. (Landolt.)

Together with phenylic acid Städeler found a series of other acids very similar to it. These are:

1. *Taurylic Acid*  $C_7H_8O$  [ $C_{14}H_8O_2$ ] ? which would be isomeric with anisol. It differs from phenylic acid by its higher boiling point, and by giving, with concentrated sulphuric acid, a fixed compound which separates in delicate white tooth-shaped masses, which gradually collect together into spherical ones.

2. *Damaluric Acid*  $C_7H_{12}O_2$  [ $C_{14}H_{12}O_4$ ]. This is an oily fluid similar to valerianic acid, heavier than water, but dissolving in it, however, to a slight extent, giving a strong acid reaction.

This acid forms, with bases, well-characterized salts. The barium salt crystallizes in prisms, often joined together into tufts, which dissolve in water, giving a turmeric brown solution. The salt is fusible, and leaves behind, after ignition, carbonate of barium in the form of the original salt; it contains 39.18 per cent. of barium.

The silver salt forms a white powder, which does not change on exposure to light; it contains 49.36 per cent. of oxide of silver.

Basic acetate of lead also gives, in the solution of damaluric acid, a white precipitate, which appears under the microscope in the form of fine prisms collected into spheres.

3. *Damolic Acid*. This acid has been least investigated of all; it is also oily, heavier than water, slightly soluble in it, and forms a crystalline barium salt, fusible on being heated, and which contains 27.50 per cent. baryta. The damolic acid salt crystallizes first out of a solution of damolurate and damolate of barium.

## DETECTION AND SEPARATION OF THESE FOUR ACIDS.

1. *Separation of the Acids collectively from the Urine.*

Fresh cow urine (80 lbs.) is mixed with calcic hydrate, boiled once, drawn off from the excess of lime, and evaporated to one-eighth. The filtrate is treated with hydrochloric acid after being well cooled, and the mother liquid, poured off from the hippuric acid, which has separated after twenty-four hours, is distilled. By repeated rectification of the milky fluid obtained by the first distillation, an oily, faint yellow liquid is finally obtained, which, for the most part, sinks to the bottom of the water in the receiver. In this oil phenylic acid can be readily detected by the reaction with ferric chloride, as well as by coloring a splinter of pine blue. The amount in human urine is very small.\*

2. *Separation of the Acids singly.*

The oil, with the water obtained, according to 1, is treated with a weighed excess of potassic hydrate, and subjected to distillation. A nitrogenous, strongly smelling oil, which has not been examined closely, is obtained in the distillate. So much sulphuric acid is added to the residue in the retort that five-sixths of the potassic hydrate used is saturated, and it is then distilled so long as a precipitate is produced in the distillate by basic acetate of lead. By repeated distillation of the fluid obtained over common salt, the greatest part of the acids are finally obtained in an oily form, and only a very small amount of an aqueous solution, with a very strongly acid reaction, remains. To separate this body with an acid reaction, the distillate is saturated with carbonate of sodium, frequently shaken, during twelve hours, and the oily layer separated from the sodium salt by extracting with ether.

a. Acids which do not form compounds with carbonate of sodium.

The ether is distilled off from the ethereal solution obtained according to 2, and the residue once more subjected to distillation with strong potassic hydrate. The potassium compound

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\* Annal. der Chemie u. Pharm., Band 97, p. 184.

which remains behind is decomposed with bicarbonate of potassium, and the distillate obtained completely dehydrated with chloride of calcium. By fractional distillation the greatest part, which consists of phenylic and taurylic acid, goes over between  $180^{\circ}$  and  $195^{\circ}$  C., and they can only be incompletely separated further by repeated fractional distillation. The chief difference between the two, besides the high boiling point of taurylic acid, lies in their behavior with concentrated sulphuric acid, with which taurylic acid unites to form a solid compound, and phenylic acid, on the contrary, forms a fluid compound.

b. Acids which form compounds with carbonate of sodium.

The solution of the sodium salt, which was freed from the phenylic and taurylic acids by ether, is evaporated, treated with sulphuric acid, and distilled. The distillate, which smells like butyric acid, separates into an oily and an aqueous layer. The whole is boiled with an excess of carbonate of barium, and allowed to crystallize. By fractional crystallization different barium salts, containing varying amounts of barium, are obtained (27 to 41 per cent. of barium). That acid is the chief constituent whose barium salt contains something over 39 per cent. (third, fourth, and fifth crystallization). This acid is the damaluric. (See Damaluric Acid.) The second acid, whose barium salt contains 27.4 per cent. (first and second crystallization), is damolic acid. (See Damolic Acid.)

The other barium salts (evaporated mother-liquor) are mixtures of damoluric acid with another barium salt: whether the acid in this salt is butyric, valerianic, or still a new one, has not yet been proved.

In its preparation from human urine, the quantity obtained is very small indeed, and if perfectly fresh urine has not been taken for the examination, a considerable quantity of acetic is always obtained.

C. *Detection of phenol in human urine.* The urine is strongly acidulated with tartaric acid, and about one-half of it is distilled off on a sand bath. The distillate obtained is shaken twice with many times its volume of ether, which extracts the phenol present. The phenol which remains behind after distilling off the ether is dissolved in a few cubic centimeters of water, and this solution is used for the above-mentioned reactions, of

which those of Landolt, Lex, and Plugge are to be especially recommended. (Salkowski.)

Landolt uses the above reaction, precipitation of the phenol as tribrom-phenol by bromine water, also for proving its presence in normal urine. If human urine (500 cc.) is directly treated with an excess of bromine water, it usually becomes turbid, and after standing several hours a brownish flocculent deposit collects at the bottom of the glass. If this is collected, washed, and treated with sodium amalgam, the unmistakable odor of phenol is apparent.

But since bromine water decomposes paraoxybenzoic acid with the formation of tribrom-phenol, and salicylic acid with bromine water yields dibrom-salicylic acid, which is decomposed by sodium amalgam, and phenol set free, Maly considers that the behavior of urine with bromine water is not sufficient proof of the preëxistence of phenol in normal urine.

According to the above-described procedure of Salkowski, phenol was detected after its internal use (0·3 to 0·9 grams per day) in every 200 cc. of urine during twenty-two days in five patients, and after its external use four times in three patients.

## § 10. URINARY COLORING MATTERS.

### I. UROBILIN. (M. JAFFÉ.)

A. *Presence.* M. Jaffé\* found urobilin in normal as well as in pathological urine, and also in the bile. This pigment is distinguished by characteristic spectroscopic properties, and also by the beautiful fluorescence which it shows under certain circumstances and by which its preëxistence in the urine can be readily verified. The high-colored urine of fever patients is especially rich in this pigment, but it was also detected in forty-five different urines of healthy individuals, so that we may well call urobilin a normal constituent of urine.

B. *Separation and Properties.* All high-colored urine of fever patients shows on spectroscopic examination† with great dis-

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\* Archiv für pathol. Anatomie, Band 47, p. 405. Zeitschrift für analyt. Chem., Band 9, p. 150, und Band 3, p. 245.

† For the method to be used in such examinations, see under the head of Blood.

tinctness, frequently only after diluting with water, an absorption band,  $\gamma$ , between the Fraunhofer lines b and F, besides a characteristic change of color on the addition of alkalies. To render the fluorescence apparent, as well as to separate the pigment from such urines, the following procedure is to be adopted. The urine is treated with a not too small excess of ammonia, filtered, and the filtrate completely precipitated with chloride of zinc solution. The voluminous red or red-brown zinc precipitate is washed first with cold and then with hot water until the chlorine reaction disappears, it is then boiled with alcohol, and finally dried with gentle heat. After pulverizing the mass, it is dissolved in ammonia, and the solution precipitated with acetate of lead. The precipitate, which is almost always intensely red, is washed with cold water for a short time, dried, and then decomposed by alcohol containing sulphuric acid. The acid solution of the pigment thus obtained has the following characteristics :

1. When concentrated it is brown, when dilute it becomes reddish yellow at first, and later rose red.

2. On spectroscopic examination of the concentrated solution the spectrum from the violet end up to about the line b is completely dark ; on dilution the darkest part gradually brightens up, and there finally remains an absorption band,  $\gamma$ , with indistinct edges between the lines b and F.

3. On the addition of ammonia the red-yellow or red color of the acid solution becomes bright yellow, and finally changes to a greenish tinge. The original specimen of urine shows the same change of color on the addition of ammonia.

4. The ammoniacal solution frequently shows a marked green fluorescence, which is brought out or strengthened by the addition of chloride of zinc.

5. The alkaline solution of the pigment shows a very characteristic absorption band,  $\delta$ , between the lines b and F, but nearer to b than the band,  $\gamma$ , of the acid solution. This band,  $\delta$ , is feeble when ammoniac hydrate is used, but stronger with sodic or potassic hydrate. The ammoniacal solution shows the band immediately with great sharpness after the addition of chloride of zinc. The band,  $\delta$ , of the alkaline solution, is much more sharply defined and darker than  $\gamma$ , and remains visible even when extremely dilute.

To separate the pigment from the acid alcoholic solution it is mixed with about an equal volume of chloroform, and then shaken with a great excess of distilled water. The separated chloroform is washed once or twice with water, and as soon as the wash water begins to be colored the operation is stopped. After distilling off the chloroform, an amorphous resinous residue of a red color remains, which dissolves in alcohol, ether, and chloroform, first with a brownish-yellow color, which on dilution becomes yellow and finally pale rose color. The solutions have a neutral reaction and show a considerable fluorescence. They give, examined with the spectroscope, the sharply defined band,  $\delta$ , like the alkaline solutions.

C. *Occurrence of Urobilin in Normal Urine.* To detect it 100 to 200 cc. of urine are precipitated with basic acetate of lead, and the washed and dried precipitate is decomposed with alcohol containing oxalic acid. If this solution still shows no absorption bands it is treated with chloroform and shaken with water. The urobilin is thus obtained without the application of heat, which is to be avoided in concentrated solution, and free from those matters which by their absorbing action on the blue and violet part of the spectrum destroy the sharpness of the band. On the addition of ammonia and chloride of zinc the acid alcoholic solution shows exquisite fluorescence, and in the spectroscope gives the band,  $\delta$ , with great sharpness.

For the preparation of the pure pigment from normal urine, the washed and dried lead precipitate from a large amount of urine is boiled with alcohol several times, and then decomposed with absolute alcohol and sulphuric acid. The solution obtained is supersaturated with ammonia, the filtrate is diluted with about an equal volume of water, and then treated with chloride of zinc. A copious precipitate of a brownish-red color is produced, while the filtrate remains quite strongly colored, but always contains only a small amount of urobilin, though large amounts of other urinary pigments. The chloride of zinc precipitate is treated as given above, with fever urine.

Jaffé further made the interesting observation that freshly passed, very pale urine, which showed no trace of an absorption band, on standing exposed to the air, often becomes darker, and then allows the dark and sharply defined characteristic band of urobilin to be recognized in the spectrum. Such urines show,



when the band,  $\gamma$ , appears distinctly, after the addition of fixed alkalies, the band,  $\delta$ , also, and ammonia and chloride of zinc occasion strongly marked fluorescence. Jaffé believes, therefore, that a chromogen of the urobilin is to be assumed to exist in the original urine, and has convinced himself, by direct experiments, that this becomes converted into urobilin with its characteristic qualities by absorbing oxygen.

We owe to Maly\* an essential increase of our knowledge of the normal urinary pigment, urobilin. He succeeded in converting the red coloring matter of the bile, bilirubin, into urobilin, with all of its characteristic qualities, by the action of sodium amalgam. For this purpose pure bilirubin is suspended in water, and small pieces of solid sodium amalgam are added gradually. If, after a time, the alkaline solution of the bilirubin becomes clearer, an excess of the amalgam is added, and if, after from two to four days, with frequent shaking, and later, after gently heating on the water bath, it becomes no clearer, the change is complete. Hydrochloric acid precipitates the coloring matter in the form of dark reddish-brown flakes from the fluid decanted from the mercury. The coloring matter, purified by repeated solution in alkalies, and precipitation with hydrochloric acid, possesses all of the qualities of urobilin. Of these, we mention the following:

1. The urobilin, or, according to Maly, hydrobilirubin, produced from bilirubin, does not give Gmelin's reaction for bile pigment.

2. The alkaline solutions vary in color from brown to the yellow of normal urine. The acid solutions vary, according to the concentration, from garnet red to brownish red and pale rose color.

3. The spectral absorption between b and F in acid solutions, its paling in ammoniacal solutions, and the intense recurrence of a dark band removed somewhat to the left, sharply defined on the left, rather indistinct on the right, after the addition of a small amount of a zinc salt to the ammoniacal solution.

4. The green fluorescence of the ammoniacal solution containing zinc, and its disappearance after the addition of an acid.

5. Its precipitation, by most of the metallic salts, in the form of brown or dark red flocculi.

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\* *Annal. der Chemie*, Band 163, p. 77.



In a similar manner biliverdin (the green pigment of bile) can be changed into urobilin by sodium amalgam.

The circulation of these pigments is, therefore, apparent. Bilirubin and biliverdin poured into the intestine with the bile, change, in their passage to the colon, by absorbing water and hydrogen, into urobilin, and, in fact, the coloring matter found in the contents of the intestine by Vaulair and Masius, stercobilin, is, according to the investigations of Jaffé,\* identical with urobilin.

Urobilin is absorbed from the intestine; it can also easily be detected on the way from the intestine to the kidneys in the circulation; at all events, the spectroscopic test was completely successful in the blood serum of the ox.

When we consider, further, that blood corpuscles in solution injected into the veins always cause an icteric urine containing bilirubin,† then the last link is no longer wanting which places in the clearest light the relations between hæmoglobin, bilirubin, and urobilin.‡ Finally, Hoppe-Seyler§ succeeded in producing a coloring matter by the action of tin and hydrochloric acid on hæmatin in alcoholic solution, which in all of its properties, chemical as well as optical, completely accorded with the urobilin of Jaffé as well as with the hydrobilirubin which Maly obtained by the action of sodium amalgam on bilirubin. Since now the same coloring matter is also produced from undecomposed hæmoglobin in alcoholic solution by tin and hydrochloric acid, there is no more doubt that the coloring matter of normal fæces and of the urine must be regarded as a product of the decomposition by reduction of the blood pigment, and that the biliary coloring matters, bilirubin and biliverdin, represent intermediate steps of this change, or at least stand in near relation to the blood pigment.

## II. UROCHROM. (THUDICHUM.)

According to Thudichum, normal urine contains only one

\* Jahresbericht d. Thierchemie, Band 1, p. 230.

† Kühne, Lehrbuch d. physiolog. Chemie, p. 89.

‡ Hoppe-Seyler has within a short time given the proof that injections of water as well as of a solution of blood pigment into the jugular vein of dogs, resulted in a considerable increase of the amount of bile pigment in the bile. (Archiv d. Physiologie, Band 9, p. 329.)

§ Bericht d. deutsch. chem. Gesellschaft, Band 7, p. 1065.

yellow coloring matter, and the resin of Prout, Scharling's omichmyloxyd, Heller's urrhodin, Schunk's indigrubin, Scherer's urinary coloring matter, also the urohæmatin of Harley, and the substance described by Marcet, are mixtures of the products of the decomposition of this yellow pigment, called urochrom by Thudichum. Maly's\* investigations have demonstrated, however, that the so-called urochrom, like the coloring matters of Scherer, contain considerable quantities of urobilin.

Thudichum† obtained his urochrom according to different methods, of which I give only one here, and in regard to the others refer to the original.

*Preparation.* The urine is treated with baric hydrate till the reaction is alkaline (to one liter of urine about five grams of hydrate of barium), and then with a saturated solution of acetate of barium. After twelve hours the precipitate is filtered off, and the filtrate completely precipitated with acetate of lead and ammonia. The washed lead precipitate is triturated in a porcelain dish with dilute sulphuric acid, the excess of acid in the filtrate saturated with carbonate of barium without the aid of heat, the filtrate is made alkaline with baryta water and treated with carbonic acid. The filtrate is now precipitated with a solution of mercuric acetate, and the precipitate obtained washed with cold and hot water. The compound of mercury thus obtained must have a yellow color; if it is gray or dark colored the treatment with acetate of lead, etc., must be repeated after decomposing it with sulphuretted hydrogen. The coloring matter is obtained by sulphuretted hydrogen in the form of a yellow solution from the urochrom-mercuric oxide made as pure as possible. This solution always contains in addition some hydrochloric or acetic acid. The hydrochloric acid can be removed by shaking with freshly precipitated oxide of silver, with which, however, a part of the urochrom combines to form a voluminous precipitate, while the fluid contains much acetate of silver. The yellow alkaline solution is finally freed from silver by sulphuretted hydrogen, and the filtrate, after evaporation on the water bath, leaves urochrom as an amorphous, solid, yellow substance.

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\* Annal. der Chemie, Band 163, p. 90.

† Brit. Med. Journ., N. S. 201, p. 509, Nov. 5, 1864. Schmidt's Jahrbücher, 1865, Band 125, p. 154.

*Properties.* Urochrom forms yellow scales, which partially dissolve in water with a pure yellow color. It is difficultly soluble in alcohol, more easily in ether, very dilute mineral acids and alkalies. The aqueous solution becomes darker on standing, finally changing to a red color, becoming turbid and depositing resinous flocculi. Heat favors the decomposition, especially in the presence of acids. Sugar is not formed. Urochrom is precipitated from the aqueous solution by nitrate of silver as a gelatinous mass soluble in nitric acid; acetate of lead gives a white flocculent precipitate. Basic acetate of lead and mercuric acetate produce a yellow precipitate. Mercuric nitrate gives a white precipitate, which on boiling becomes a pale flesh-color, while the supernatant fluid is colored rose red. By oxidation in the air there is first formed from the urochrom a red substance, which corresponds to uroërythrin, and to which the red urine of disease owes its color. Under the influence of acids, the yellow soluble, as well as the red substance, yields three insoluble products, which are deposited from an acid solution of urochrom after the addition of water, by sufficiently long boiling, in brown clumps which collect together in balls. On treating this deposit with alcohol, a brown powder soluble in potassic hydrate, from which it can be precipitated by acetic acid, uromelanin,\* remains behind. The beautiful ruby-red alcoholic solution yields by precipitation with water a red resin, which can be decomposed by ether into two bodies. The ethereal solution has a very beautiful red color and contains a resinous acid, omicholic acid, corresponding to the omichmyloxyde. A yellow substance remains behind insoluble in ether, uropittin, which is obtained in the crystalline form from absolute alcohol, and on analysis gives the formula  $C_9H_{10}N_2O_3$  ( $C_{18}H_{10}N_2O_6$ ).

Uropittin and uromelanin can also be obtained directly from the urine. Fresh urine is treated, drop by drop, with concentrated sulphuric acid, and the filtrate evaporated in a retort to one-half. After cooling, a black resin separates, from which, after washing and drying, uropittin is extracted by alcohol, while uromelanin remains behind.

According to Thudichum, the odor of decomposed acid or

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\* Journ. f. pr. Chem., Band 104, p. 257.

alkaline urine comes from omicholic acid and uropittin, or the products of their decomposition; it is rendered stronger by carbonate of ammonium, but is not caused by it. The urine contains, moreover, a volatile ethereal oil, which is colored red by boiling with mercuric nitrate, and also cresyl alcohol. Urochrom, retained in the blood, is one of the characteristics of uræmia; it is decomposed in the blood to uropittin and omicholic acid, which can be recognized again in the tissues, in the deposit on the teeth, and in the stinking breath. If the coloring matter is retained in the blood, the typhoid symptoms of uræmia predominate. Normal urine contains, according to Thudichum, no indican; but this body and the products of its decomposition, with all of their characteristic properties, have been so frequently found in the urine by different investigators, that it may well be a question what is normal urine.

### III. UROXANTHIN. (HELLER.)—INDICAN. (SCHUNCK.)

Heller calls a substance which occurs in normal urine in small amount, in diseased urine, however, in large amount, uroxanthin. It imparts to the urine, when abundant, an intense light-yellow color, and possesses the noticeable property of yielding by the action of acids, etc., with the separation of a saccharine substance, two new pigments, uroglauclin and urrhodin. According to the investigations of Schunck, Hoppe-Seyler and others, this body is nothing else than indican. Hoppe found it most abundantly in the urine in carcinoma of the liver, but it is also abundant in the urine of dogs. Oscar Wyss\* detected considerable quantities of indican in the urine first passed after an attack of cholera. Jaffé† found a considerable increase of indican in the urine after subcutaneous injections of indol, a fact which is the more interesting, since, according to Kühne's investigations, indol belongs to the products of pancreatic digestion in the alimentary canal, and M. Nencki‡ obtained it directly from blood albumen, in considerable quantity, by the action of pancreatic ferment. The greatest part of the indol, indeed, is passed off with the fæces, and imparts to them their

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\* Archiv der Heilkunde, Band 9, p. 232.

† Centralblatt f. d. med. Wissenschaften, 1872, No. 1.

‡ Bericht der deutsch. chem. Gesellschaft, Band 8, p. 836.

characteristic odor ; another part is absorbed, and uniting with a saccharine substance, is eliminated with the urine as indican. If the separation with the excrement is impeded, a greater resorption may be expected, and, in fact, Jaffé found, in a fatal case of incarceration of the small intestine, enormous amounts of indican in the urine.

Rosenstein\* found a considerable increase of indican in Addison's disease, and Jaffé† found it in all diseased processes which cause obstruction of the small intestine.

This mother substance of indigo is decomposed very readily in contact with sulphuric acid, hydrochloric acid, etc. The coloring matters, indigo blue, indigo red, etc., separate, while a saccharine substance which reduces the oxide of copper, indigluclin,  $C_6H_{10}O_6$  [ $C_{12}H_{10}O_{11}$ ], leucin, and volatile fatty acids (acetic acid, formic acid, etc.) remain in solution. The same decomposition is brought about by ferments, especially by the decomposition of the urine ; indigo white is formed, which becomes blue when exposed to the air, hence putrefying urine frequently shows a bluish-red, metallic, shining pellicle on the surface.

Indican is precipitated from its solution by an ammoniacal solution of acetate of lead.

*Preparation.* Fresh urine is precipitated with basic acetate of lead, filtered and precipitated with ammonia. The second precipitate is filtered off, washed, suspended in alcohol, and decomposed by sulphuretted hydrogen. The filtrate is then first evaporated at a gentle heat, and finally over sulphuric acid in a vacuum. The indican thus obtained is still rendered somewhat impure by sugar. For its further purification it is dissolved in water, shaken with freshly precipitated hydrated oxide of copper, filtered, the filtrate treated with sulphuretted hydrogen, precipitated with ether, and the fluid filtered off and evaporated best in a vacuum. The indican thus remains behind as a clear brown syrup. (Hoppe-Seyler.)

#### IV. UROGLAUCIN AND URRHODIN.—INDIGO BLUE AND INDIGO RED.

These substances sometimes occur in the sediment of patho-

\* Virchow's Archiv, Band 56, p. 27.

† Centralblatt f. d. med. Wissenschaft., 1872, No. 81.

logical urine. They are, as above remarked, according to Heller, the products of the oxidation of uroxanthin, according to Schunk they are most probably the products of the decomposition of indican.

a. *Urrhodin* (indigo red). The ethereal solution after evaporation leaves the pigment behind in a solid form, but non-crystalline. Indistinct crystals are obtained, however, on very slow evaporation of an alcoholic solution. Urrhodin appears crystallized almost black or in very thin layers carmine red. It appears in the form of rose-red granules when amorphous. It dissolves in alcohol and ether with a beautiful red color, but is insoluble in water.\*

After the ingestion of oxindol and dioxindol, these bodies do not appear again in the urine of men, dogs or rabbits. Yet when the urine was heated with hydrochloric acid and extracted with alcohol and ether, red coloring matters were constantly obtained in small quantity, which had a resemblance to those which are obtained by the oxidation of aqueous solutions of oxindol and dioxindol in the air. (M. Nencki and Massow.) After the internal use of isatin, however, a pigment is obtained both from dog and human urine, which corresponded with a pigment, which Nencki† obtained from the urine of a woman suffering from paralysis of the cervical part of the spinal cord, and which appears to be identical with indigo red (urrhodin).

b. *Uroglaucin* (indigo blue). Uroglaucin appears as a blue powder which consists of microscopic needles terminating in a fine point, but which seldom occur isolated, being usually collected together in groups of two, three, or several. They frequently form star or circular-shaped groups, which are again joined together and present large clumps of radiating bodies. Indigo blue is capable of sublimation, and can be reduced by sulphate of iron, etc. It is often found in the urine in degeneration of the kidney, and at times, according to Virchow, in the crystalline form. In putrefying urine it occurs as a product of the decomposition of indican. Such a urine frequently becomes blue on shaking with air, and on standing a blue iridescent pellicle forms on the surface, in which, at times, microscopic

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\* Heller's Archiv, 1846, p. 21.

† Berichte d. deutsch. chem. Gesellschaft, Band 7, p. 1593.

needles of indigo can be recognized. (Hoppe-Seyler.) The addition of hydrochloric or nitric acid frequently separates it from the urine mixed with uric acid as a precipitate, which is gradually deposited.

These products of the decomposition of indican can be obtained from the urine by different methods.

A. *Preparation* by the method of Schunck. The urine is treated with basic acetate of lead as long as a precipitate occurs, filtered, and the filtrate precipitated with an excess of ammonia, by which the indican (uroxanthin) is precipitated in combination with oxide of lead. The precipitate, collected and washed, is decomposed completely by cold dilute hydrochloric or sulphuric acid, and the solution is filtered. If there is much indigo-forming material present, the filter and precipitate, and also the surface of the brown filtrate, are colored with a blue substance; if there is but little present, the blue pellicle is formed only after twenty-four or forty-eight hours on the filter, never later. The brown filtrate, after removal of the indigo blue, which gradually separates, deposits on boiling a dark brown powder, which has the same appearance as that which can be obtained directly from the extractive matter of the urine by boiling it with acids, and which partly dissolves in sodic hydrate with a brown color and partly remains undissolved. The undissolved portion is separated into two bodies by boiling alcohol, one of which dissolves in it with a purple-blue color, and appears to be identical with indigo red, the other has the characteristics of indigo blue.\*

B. *Preparation* by the method of Kletzinsky and Keller. Urine, which is colored blue by mixing with fuming hydrochloric acid, is completely precipitated by basic acetate of lead, and the filtrate, freed from the excess of oxide of lead by sulphuretted hydrogen, is evaporated to one-third. The fluid, while still warm, is allowed to flow into two or three times its volume of fuming hydrochloric acid, and allowed to stand a few days, during which time a thin, coppery-red, iridescent pellicle forms on the surface of the mixture, and the fluid gradually becomes cloudy. It is filtered, the bluish-black mass which is separated is washed completely with water, and treated with ether after

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\* Journ. f. pr. Chem., Band 75, p. 878.



drying over sulphuric acid; the ether becomes dark red or purple, and contains a red, amorphous, resinous mass, urrhodin (indigrubin, according to Schunck). The residue left by the ether is then boiled with alcohol, and the deep bottle-blue solution is left to itself in closed flasks. After some months a velvet-black sediment has deposited, which frequently contains rudimentary crystals (the elementary analysis of this precipitate corresponds, according to Kletzinsky, with that of indigo blue). In urine which is very rich in indican there is no need, according to my experience, of this detailed manipulation; such a urine, on mixing an equal volume of hydrochloric acid, very soon deposits the pigments. The amount obtained is always very small, and with less than ten to twenty pounds of urine the work should not be undertaken.

C. *Detection*.—1. The following very pretty reaction of Heller serves for the detection of even small amounts of indican. Three to four cc. of strong fuming hydrochloric acid are mixed in a test tube with thirty or forty drops of the urine to be tested, or the urine, after the addition of a little hydrochloric or nitric acid, is heated to boiling. If indican is present the mixture is colored from a reddish violet to intense blue by the decomposition of this body. If with small amounts of indican the reaction fails, it can be made far more delicate by the addition of two or three drops of strong nitric acid. There results from this refinement of the test, not immediately but in a few minutes, a beautiful violet color, which first plays rather into blue, but later rather into red, and sooner or later becomes dirty red, and at last yellow again. The color appears almost always without the addition of nitric acid, but the latter enables us to detect the least traces of indican. Indican suffers in this reaction as in the others a decomposition into indigo blue, indigo red, and sugar.

2. Ten cc. of the urine to be tested for indican are treated with an equal volume of hydrochloric acid, and then a saturated solution of calcic hypochlorite is added drop by drop. The mixture becomes, according to the amount of indican present, red, violet, green, or blue, but after filtering, under all circumstances, it leaves behind on the filter a distinct blue tinge. (Jaffé.)\*

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\* Archiv der Physiolog., Band 3, p. 448.



3. According to Stockvis the urine to be tested should be warmed with two parts of impure nitric acid to 60° or 70° and shaken with chloroform or ether. Both solutions are then quickly colored violet blue, and show, when placed before the slit of the spectroscope, the characteristic absorption bands of indigo blue between C and D.

The solutions of sulphindigotic acid give, on spectroscopic examination, a sharp, dark absorption band between the lines C and D, which reaches beyond D when the solution is more concentrated.

I have had an opportunity here to observe a urine very rich in indican, for a long period. It was secreted at different times, and for a long period uninterruptedly by a young man eighteen to twenty years of age of apparently healthy constitution.

This urine, treated with about an equal amount of hydrochloric or nitric acid, soon became violet, then darker, and at last a deep, dark blue. After shaking and standing awhile the pigment separated either as a deep blue scum or as a thin, reddish-blue, iridescent pellicle.

The washed coloring matter consisted of a deep blue powder with a copper-red streak, which dissolved in boiling alcohol, but on cooling separated, for the most part, again, while the supernatant fluid remained colored violet or reddish (urrrhodin).

The product thus obtained could be sublimed at a moderate heat, when it first gave rise to beautiful red fumes, and then was deposited as a reddish-brown sublimate. Seen under the microscope it shows the above-mentioned groups of needles. This sublimate could not be distinguished from sublimed indigo, and also its behavior to concentrated sulphuric acid, nitric acid, and especially reducing agents, such as ferrous oxide, sulphide of ammonium, etc., completely corresponded with that of indigo.\*

The pigment was entirely destroyed by evaporating the urine, so that it was no longer capable of demonstration in the residue. Nitrous acid destroyed it also.

It remains for me to call attention to a peculiar behavior of this urine toward concentrated sulphuric acid: if a small amount of it was treated with a sixth or a fourth of its volume of con-

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\* *Annal. d. Chem. u. Pharm.*, Band 90, p. 120.

centrated sulphuric acid, without mixing, there occurred, first, at the point of contact of the two fluids, a red coloration, which always became darker, the color finally spread through the whole mass, and the fluid became a deep, dark red, which changed to a purple violet. This play of colors was perfectly similar to that which jaundiced urine yields on treating with sugar and sulphuric acid; yet here the color appeared without the addition of sugar, and failed to appear when the pigment was decomposed by evaporation.

Although indican occurs very frequently in normal urine, at least in small amount, yet it is not improbable that it can be increased, in certain diseases, so as to form a symptom of the disease, and, therefore, it well deserves the attention of physicians. At all events it is of great interest to recognize indican, that is, indigo blue, etc., as a probable product of the decomposition of protein matters, which is rendered more likely by the fact that the products of decomposition of indican include among others, as above remarked, in addition to a saccharine substance, both leucin and volatile fatty acids.

Relatively very large amounts of indigo are obtained from the urine of the horse and cow. Creasote and oil of bitter almonds, even taken in small doses, are said to increase the amount of indigo in the urine very much. (Kletzinsky.)

It is readily seen that by the combination of urobilin with varying amounts of urrhodin and uroglauclin, very manifold shades of color in the urine (greenish, grass green, violet, reddish) can result.

#### V. UROERYTHRIN.

That coloring matter is called uroerythrin which imparts to sediments of uric acid and urates their brick-red or rose-red color, and which, on contact with the air, increases considerably. Uroerythrin is said also to occur in solution in pathological urine, to which it imparts a red color. According to Thudichum, it probably is the result of the oxidation of normal urochrom.

The red sediments which occur so frequently appear, however, to contain at least two different pigments, since according to Hoppe many sediments yield to chloroform a beautiful pur-

plish-red pigment soluble in alcohol, while according to Heller uroërythrin is insoluble in alcohol. According to Heller, alcohol only extracts from the sediments urrhodin (indigo red) and uroglaucin (indigo). According to Jaffé, urobilin (see above) is not identical with the pigment of these sediments. Even if in many sediments urobilin undoubtedly occurs, it appears to be completely wanting in others, or to exist in common with one or several other pigments by which its entire demeanor is altered.

#### VI. BLACK URINE.

J. Vogel found a dark-colored urine after breathing arseniuretted hydrogen. Waldenström, Almén, Salkowski, Bartels,\* and others observed after inunctions of tar, but especially after the external as well as internal use of carbolic acid, tarry-looking, almost black urine. According to Waldenström, Salkowski, and Almén,† carbolic acid can be detected in the urine in the latter case.

Maly‡ did not succeed, however, in such cases in detecting phenol in the distillate. The dark color spoken of does not seem to occur in the bladder, but first appears on exposure to the air. According to the observations of Maly, the browning or blackening first appears as a zone in the upper layer of fluid, which gradually descends from above downward, when the urine remains at rest.

#### § 11. KRYPTOPHANIC ACID.

According to the investigations of Thudichum,§ kryptophanic acid discovered by him is the normal free acid of the urine. (?) *It forms the chief mass of the so-called extractive matter, and is obtained from normal urine in the following manner :*

The urine is made alkaline with milk of lime, filtered, evaporated, then acidulated with acetic acid and concentrated until the salts, etc., crystallize out. The syrup decanted from the

\* Oral communication.

† Neues Jahrb. f. Pharm., Band 84, p. 113.

‡ Jahresbericht u. d. Fortschritte der Thierchemie, 1871, p. 184.

§ Centralbl. f. d. med. Wissenschaft., 1870, p. 195 and 209. Zeitschr. f. analyt. Chemie, Band 10, Heft 1.

crystals is shaken in a flask with five times its volume of 90 per cent. alcohol, when impure kryptophanate of calcium separates, which is repeatedly washed with alcohol. To purify it, the crude calcium salt is dissolved in water, and precipitated with a large excess of a saturated solution of acetate of lead. It is filtered and five or six times its volume of strong alcohol is added to the filtrate, by which white neutral kryptophanate of lead is precipitated. The precipitate is collected on a filter, washed with alcohol, then with a little water, and lastly with ether; it is dried in a vacuum and finally decomposed with a sufficient amount of sulphuric acid. For its further purification the acid is saturated with baryta water, the excess of barium is removed by carbonic acid, the kryptophanate of barium precipitated with alcohol, again dissolved in water and once more precipitated with acetate of lead in excess. The filtrate which now results yields, after the addition of alcohol, pure, white, neutral kryptophanate of lead. To obtain the free acid the lead salt is decomposed with sulphuric acid.

The product thus obtained is amorphous, gummy, transparent, soluble in water, less so in alcohol, and least in ether.

Thudichum attributes to his new, long-hidden acid a great physiological as well as pathological significance, but further investigations must yet decide whether this is really a pure substance, which from the mode of preparation is somewhat doubtful.

J. Pircher\* and A. Silversidet† could not convince themselves of the existence of kryptophanic acid. Both investigators arrived at no decisive result. Hlasiwetz and Habermann,‡ however, suppose that Thudichum's kryptophanic acid is only an impure glutamic acid, which also, like kryptophanic acid, reduces cupric oxide in alkaline solution, and whose formula ( $C_5H_7NO_4$ ) corresponds with that of kryptophanic acid ( $C_5H_7NO_4$ ) within one atom of oxygen. Further investigations upon this substance are, therefore, very much to be desired; certainly the occurrence in the urine of glutamic acid, an interesting product of the decomposition of animal as well as vegetable albuminoid bodies, would be of great physiological interest.

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\* Centralblatt f. d. med. Wissenschaft., 1871, No. 4.

† Journ. of Anat. and Physiol., vol. vi., p. 422.

‡ Annal. d. Chem. u. Pharm., Band 159, p. 150.

## B. Inorganic.

## § 12.

The urine contains of the inorganic bases especially sodium, potassium, calcium, and magnesium, partly combined, especially the first two, with uric and hippuric acids, but also with sulphuric, phosphoric, hydrochloric, and nitric acids. Besides these, small amounts of iron and silicic acid, finally also ammonium salts, especially in alkaline urine. The urine does not contain free gases except carbonic acid, nitrogen, and traces of oxygen; pathologically, however, sulphuretted hydrogen sometimes occurs. The whole amount of non-volatile salts contained in the urine differs in different persons and under different pathological conditions very much. Thus in men variations of from 9.06 to 24.50 grams occur, in women from 10.28 to 19.63 grams. Lehmann found in his own urine daily, while on a mixed diet, 15.245 grams (varying between 9.652 and 17.284 grams).\*

## § 13. CHLORIDE OF SODIUM.

A. *Presence.* We may assume that almost all of the chlorine occurring in urine is in combination with sodium. The amount of chloride of sodium secreted varies in different persons and at different times of the day.

Hegar has communicated observations on the variations in the amount of chloride of sodium in eight persons, the results of which are briefly as follows: On an average the chlorine separated in twenty-four hours amounted to 10.46 grams, corresponding to 17.5 grams of chloride of sodium. The secretion of chlorine is the greatest in the afternoon; at night, however, it diminishes considerably and rises again in the morning. Physical exercise increases, and slight disturbance of the health diminishes the secretion quite rapidly. The amount is rapidly

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\* E. Weidner. Investigations of normal and pathological urine, especially in regard to the proportion of lime, magnesia, potassium, sodium and iron to the other constituents of the urine. Rostock bei Adler's Erben, 1867. E. Salkowski, investigations concerning the secretion of the alkaline salts. Virchow's Archiv, Band 58, p. 208.

increased by drinking water, but it diminishes later so much the more. After taking beer the amount of chlorine is unusually small. With regard to the whole amount of chloride of sodium separated in twenty-four hours, the observations of Bischoff\* differ somewhat from the statement of Hegar. He found in his own urine, in twenty-four hours, between 8.64 and 24.48 grams, and gives as the average 14.73 grams.

The amount of chloride of sodium is extraordinarily diminished in many diseases, indeed, in all in which abundant exudations take place from the blood. Redtenbacher saw in inflammations of the lungs the amount of chlorine often diminished to a minimum, so that in some cases no cloudiness at all could be observed after adding nitrate of silver.

*B. Microscopic Properties.* Chloride of sodium crystallizes under the microscope in extraordinarily beautiful, regular, stair-like cubes. It suffers a peculiar modification when it crystallizes from a solution which contains urea at the same time; the ordinary cubes are thereby changed into octahedral and tetrahedral forms.

*C. Chemical Properties.*—1. If water is poured over pure, coarsely crushed, crystalline rock-salt, and the fluid, after a thorough shaking, is allowed to stand twenty-four hours at 12° to 50° C., an invariable amount of salt is dissolved. In 10 cc. of this clear filtered solution Liebig and others found, as an average of many very nearly coinciding estimations, 3.184 grams of common salt.

2. Nitrate of silver produces, in all fluids which contain chloride of sodium, a white caseous precipitate of chloride of silver, insoluble in nitric and hydrochloric acids. If the urine, however, after it has been acidulated with nitric acid, is treated with a solution of nitrate of silver, the precipitate which results is never pure chloride of silver, but the pigments, uric acid, etc., are also precipitated by the silver salt, and in the quantitative estimation of chlorine by nitrate of silver this is not to be disregarded.

3. If a concentrated solution of chloride of sodium is mixed with a concentrated solution of mercuric nitrate, the two salts quickly undergo mutual decomposition, nitrate of sodium is

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\* Bischoff, Urea, 1858, p. 28.

formed, and the fluid solidifies to a crystalline mass of corrosive sublimate. The same decomposition takes place in dilute solutions also, only the corrosive sublimate formed does not separate, but remains in solution in the fluid.

We have seen under urea, that in a solution of this substance, which is feebly acid or neutral, mercuric nitrate produces a precipitate of urea with mercuric oxide. Corrosive sublimate, on the contrary, produces no precipitate in acid or neutral solutions of urea. After this premise it will be easy to understand the following reaction, which Liebig has made use of for the quantitative estimation of chloride of sodium in the urine. If the phosphoric and sulphuric acids are removed from specimens of urine by the addition of nitrate and hydrate of barium, and if the alkaline filtrate is made neutral again or feebly acid by nitric acid, the fluid is a weak acid solution of chloride of sodium with urea. If now we treat this with a dilute solution of mercuric nitrate, drop by drop, a white precipitate will occur at the point of contact of the two fluids, which, however, disappears again on stirring the mixture. The precipitate which first takes place is the compound of urea-mercuric oxide. But, since chloride of sodium is in the fluid, the mercuric nitrate is immediately changed to corrosive sublimate, which, as is known, does not precipitate urea in feebly acid solutions. Therefore, the precipitate which first occurs disappears, and the fluid becomes as clear as before. This play of reactions is repeated in the same way until all of the chloride of sodium present has been used up in changing the mercuric nitrate into corrosive sublimate. At last it ceases, another drop of the mercuric nitrate solution finds no more chloride of sodium by which it can be changed into corrosive sublimate, and a permanent precipitate of urea-mercuric oxide is produced. If the amount of the mercuric nitrate solution which has been added up to this point is known, the amount of chloride of sodium which was present can be readily reckoned, since one equivalent of mercuric oxide corresponds to just one equivalent of chloride of sodium.

4. If a neutral solution of chloride of sodium, which at the same time contains phosphate of sodium, is treated with a few drops of a neutral solution of chromate of potassium, and a solution of nitrate of silver is allowed to flow into it, drop by drop, from



a pipette, all of the chlorine will be first precipitated as chloride of silver. When this point has been reached, the next drop of the silver solution gives a permanent red color, due to chromate of silver. The phosphoric acid remains completely in solution up to this point, since the silver salt precipitates these three acids in the following succession: chlorine, chromic acid, phosphoric acid. (Mohr's volumetric method.)

D. *Detection.* The reaction with nitrate of silver already given always serves for the recognition of chloride of sodium in the urine. But the urine contains phosphoric acid, and this also gives, with oxide of silver, a precipitate of phosphate of silver, which, however, is soluble in nitric acid, while chloride of silver is not soluble in this reagent. We must, therefore, in testing urine for chlorine, add to it, either before or after the addition of the silver solution, nitric acid enough to give a strong acid reaction. In the first case the phosphate of silver will not then be precipitated, but in the second it will dissolve again directly, and only the chloride of silver remains in caseous flakes.

If the urine is evaporated to a syrupy consistence, the chloride of sodium crystallizes out after a time in cubes or octahedra, which can easily be recognized. The spectroscopic test, obtaining the yellow sodium flame, serves for the direct recognition of the sodium.

#### § 14. CHLORIDE OF POTASSIUM.

The urine, together with chloride of sodium, contains chloride of potassium, which has the same crystalline form as chloride of sodium. To detect the potassium in urine it is treated with a little hydrochloric acid, an equal volume of a mixture of alcohol and ether is added, and afterward a solution of chloride of platinum. After a few hours the potassio-platinic chloride, mixed with ammonio-platinic chloride, will have separated in beautiful octahedra, which are readily recognizable under the microscope.

Tartaric acid can also be used with advantage. 100 to 150 cc. are evaporated to one-eighth of the original volume, allowed to cool, filtered, and the filtrate treated with a concentrated solution of tartaric acid in excess. After standing ten hours in



a cool place the separation of acid tartrate of potassium is complete. Salkowski \* obtained by this method from 500 cc. of urine 2·7 to 3 grams of cream of tartar.

Weidner † found in his own urine, on an average, 3·91 grams of potassium in twenty-four hours. The maximum amounted to 5·9 grams, the minimum 2 grams. The relative proportion of potassium and sodium was 1:1·35. ‡

### § 15. SULPHATES.

*A. Presence.* Many experiments have been undertaken, under the direction of Vogel, concerning the amount of sulphates in the urine. From these determinations it has been proved that an adult passes, on an average, 2·094 grams of sulphuric acid in twenty-four hours, which coincides with the more recent investigations of Weidner, who found on the average 2·1 grams.

During the time of digestion the amount of sulphuric acid secreted increases, it sinks somewhat in the night, and reaches its minimum in the forenoon hours. The secretion increases for a short time on copious drinking of water, but later decreases all the more. (Gruner.) Sulphates taken into the economy are completely separated again with the urine in from eighteen to twenty-four hours. Pure sulphur also increases the amount of sulphuric acid in the urine. Without doubt the sulphur of the protein substances ingested with the food is gradually oxidized to sulphuric acid in the blood, and is then eliminated with the urine, combined with alkalies. Therefore, after an abundant meat diet, not only the urea, but also the sulphuric acid is found increased in the urine. Disease, also, frequently exercises a decided influence on the excretion of sulphuric acid, so that it is often increased and often diminished.

*B. Chemical Properties.* Some of the sulphates are soluble in water, and some insoluble. The sulphates of the alkalies and alkaline earths are not decomposed by a red heat; if, however, they are heated with charcoal or organic matters which yield charcoal on being heated, they undergo a reduction to free sul-

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\* Archiv d. Physiologie, Band 2, Heft 351.

† Loc. cit.

‡ Investigations of the secretion of alkaline salts by E. Salkowski, Virchow's Archiv, Band 58.

phur, which can be recognized by the odor of sulphuretted hydrogen, if the red-hot mass is moistened with a little acid. If this test is made on polished silver a black spot is produced.

1. Chloride of barium produces, in solutions of the sulphates, a white, fine pulverulent precipitate of sulphate of barium, insoluble in nitric and hydrochloric acids.

2. Acetate of lead precipitates sulphate of lead.

3. If organic matter and sulphates are moistened and exposed to a tolerably high temperature, sulphuretted hydrogen is formed. It is possible that the sulphuretted hydrogen, at times occurring in the urine, is formed in this manner.

C. *Detection.* Sulphuric acid gives, with barium salts, a precipitate insoluble in acids, and apparent, even when very dilute; in testing a urine for sulphuric acid, therefore, we make it strongly acid with nitric or hydrochloric acids, for the reasons given under chloride of sodium, and then treat it with a solution of chloride or nitrate of barium; any precipitate which takes place (sulphate of barium) points with certainty to the presence of sulphuric acid.

## § 16. ACID PHOSPHATE OF SODIUM.

A. *Presence.* This salt, according to Liebig's investigations, without doubt occurs in the urine, and is also in most cases the chief cause of its acid reaction.

Many determinations of the amount of phosphoric acid in the urine have been made by Breed.\* The average excretion of phosphoric acid in twenty-four hours in a number of persons was from 3.765 grams to 5.180 grams. This daily amount of phosphoric acid, however, appears to me to be somewhat too high according to the numerous determinations given in recent times, which is to be attributed to the very defective method of determination with ferric chloride, which has hitherto been used. According to the volumetric method with oxide of uranium solution, first proposed by me for the determination of the phosphoric acid in the urine, I have seldom found more than two grams of phosphoric acid in twenty-four hours under normal conditions. Weidner found the maximum was 3.8, the

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\* Ann. d. Chem. u. Pharm., Band 78, p. 150.

minimum 2.25, and the average 2.76 grams. Increased drinking augments the secretion a little, yet, according to Winter, only during the first three or four hours. Winter also found that at night considerably more phosphoric acid is secreted than in the morning, but most of all at midday, and both Winter and Breed observed that the amount of phosphoric acid very considerably increased after taking food. The variations in disease are tolerably great, as is readily understood; according to Heller, it should keep tolerable pace with the sulphates.\*

*B. Chemical Properties.*—1. The acid phosphate of sodium is readily soluble in water and gives to it an acid reaction. On heating it to a red heat alone it is not decomposed, but if it is at first very intimately mixed with charcoal, or ignited with organic matters, a part of the phosphoric acid is reduced, and phosphorus is formed which is immediately volatilized.

2. Chloride and nitrate of barium give in solutions of phosphate of sodium a precipitate of phosphate of barium, which is readily soluble in acids.

3. Phosphoric acid forms compounds with calcium and magnesium which are insoluble in water, but are soluble even in acetic acid without decomposition. In the urine we find phosphate of calcium and phosphate of magnesium, which are held in solution by the free acids or acid salts. If we neutralize the urine with ammonia, the phosphate of calcium is precipitated unchanged, the phosphate of magnesium, however, takes up ammonium and appears as ammonio-magnesian phosphate in the precipitate.

The formation of these compounds, which occur in alkaline urine as a sediment, depends on this. The alkaline reaction of a urine comes mostly from carbonate of ammonium produced by the decomposition of urea; but as soon as this has formed the free acid of the urine disappears, and the earthy phosphates can no longer be held in solution. The phosphate of calcium then separates usually in the amorphous form, but the phosphate of magnesium separates in beautiful crystals as ammonio-magnesian phosphate.

4. Ferric chloride gives, in solutions of the phosphates which are acidulated with free acetic acid, a yellowish-white, gela-

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\* See Weldner, loc. cit.

tinuous precipitate of phosphate of iron. This compound is soluble in all acids except acetic, therefore a solution from which we wish to precipitate the phosphoric acid by ferric chloride must contain no other free acid. If, however, any other free acid is present, acetate of sodium and free acetic acid are added to the fluid before the precipitation with ferric chloride; in this way the solution is rendered acid with acetic acid, in which the phosphate of iron is insoluble.

5. If a phosphate is dissolved in water or acetic acid and treated with acetate or nitrate of uranium, a yellow precipitate of phosphate of uranium immediately takes place. The precipitate does not dissolve in water and acetic acid, but does in the mineral acids, from which it may again be completely precipitated by a sufficient excess of alkaline acetates and heat. We make use of this reaction for the volumetric estimation of phosphoric acid.

*C. Detection.* (See § 17.)

## § 17. PHOSPHATES OF CALCIUM AND MAGNESIUM.

As above remarked, these two earthy phosphates are in solution in acid urine, but they are separated from it as soon as it is rendered alkaline. A long series of observations, which I commenced on the secretion of the earthy phosphates in four healthy young men, gave the following results:

1. In the normal condition there was passed by an adult male from twenty to twenty-five years of age, on a mixed diet, in twenty-four hours, as a mean of fifty-two observations, 0.9441 to 1.012 grams of earthy phosphates.

The maximum amounted on the average to from 1.138 to 1.263 grams; only once was 1.554 grams passed in twenty-four hours.

The minimum amounted to an average of 0.8 gram, and once only 0.328 gram was passed.

2. The phosphate of calcium amounted on an average of fifty-two estimates to from 0.31 to 0.37 gram. The maximum averaged 0.39 to 0.52 gram; only once was 0.616 gram passed.

The minimum was tolerably constant at 0.25 gram; once only it amounted to 0.15 gram.

3. The phosphate of magnesium amounted on an average

of fifty-two observations to 0.64 gram. The maximum averaged 0.77; only once 0.938 gram was passed. The minimum amounted in the average to 0.5, but sank once to 0.178 gram.

4. In the normal condition on the average about one equivalent of  $3\text{CaO},\text{PO}_3$  to three equivalents of  $2\text{MgO},\text{PO}_3$  is passed. In one hundred parts of earthy phosphates 67 per cent. consist of phosphate of magnesium, and 33 per cent. of phosphate of calcium.

5. Calcium salts ingested do not pass out in the urine, or only in very small amount; the whole amount of phosphates secreted normally does not thereby suffer any very great increase.

6. In disease the absolute amount of earthy phosphates, as well as the relative proportion between calcic and magnesian phosphates, departs much from the normal secretion.

*Detection.* The recognition of phosphoric acid in acid urine presents no difficulties; the precipitate which takes place immediately upon the addition of ammonia, and consists of earthy phosphates, leaves no doubt of its presence. It can readily be determined if the urine contains any more phosphoric acid than was precipitated with the calcium and magnesium, by filtering off the ammonia precipitate, and testing the filtrate acidified with acetic acid with uranium solution; the formation of a yellowish-white precipitate will show the amount of the phosphoric acid which remains. In an alkaline urine we find the earthy phosphates in the sediment, and will refer to them under that head. If we wish to separate the calcium from the magnesium in the precipitate which takes place on the addition of ammonia, and which consists of the phosphate of calcium and ammonio-magnesian phosphate, we dissolve the precipitate in acetic acid, add a little chloride of ammonium, and then a solution of oxalate of ammonium, by which the calcium is precipitated as oxalate, while the magnesium remains in solution, and can be precipitated from the filtrate by the addition of ammonia again as ammonio-magnesian phosphate.

## § 18. IRON.

*A. Presence.* Iron for the most part is found only in very minute quantity in the residue of urine after ignition. If a

urine contains blood, iron is more easily detected in the ash.

According to the investigations of Magnier\* the amount of iron in a healthy man of medium weight varies between 0.003 and 0.011 gram in a liter. A mean of fourteen examinations gave 0.007 gram of iron to the liter of urine.

### B. *Chemical Properties.*

1. Sulphide of ammonium yields in ferrous and ferric solutions a black precipitate of sulphide of iron, which is readily soluble in hydrochloric and nitric acids.

2. Ferrocyanide of potassium yields in ferric solutions a deep blue precipitate of ferrocyanide of iron (Prussian blue). In ferrous solutions the precipitate is bluish white, and consists of ferricyanide of potassium and iron.

3. Sulphocyanide of potassium does not change ferrous solutions, but it produces the intensely red sulphocyanide of iron in ferric solutions.

4. If a solution of permanganate of potassium is added to an acid solution of a ferrous salt, the ferrous oxide becomes converted into ferric oxide, and when this point is reached, the next drop of the permanganate of potassium solution causes a beautiful red coloration of the fluid.

C. *Detection.* The ash of the residue of urine is always chosen for the isolation and detection of iron. It is dissolved in a little hydrochloric acid, and the solution divided into two parts. The first half is boiled with a drop of nitric acid and treated with sulphocyanide of potassium; if there is the least amount of ferric oxide present, the fluid will assume a reddish color, which becomes a deep dark red when it is in greater amount. With mere traces of ferric oxide, the color is seen most distinctly when the test tube is placed on a white surface and examined from above. If, instead of sulphocyanide of potassium, ferrocyanide of potassium is added to the second portion after boiling with nitric acid and diluting, flocculi of Prussian blue separate after standing a time. If the amount of iron is more considerable the Prussian blue is immediately precipitated.

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\* Berichte d. deutsch. chem. Gesellschaft, Band 7, p. 1796.

## § 19. AMMONIUM SALTS.

It is a well-known fact that the detection and estimation of the ammonium salts in normal urine is attended with many difficulties. The readiness with which the coloring and extractive matters decompose, and the urea becomes converted into carbonate of ammonium, especially if the above matters are present, is well known. This is the reason that we continually find different statements concerning the occurrence and amount of the ammonium salts in normal urine. If normal acid urine is concentrated in a retort at as low a temperature as possible, ammonia will always be found in the distillate, while the concentrated urine which remains behind often reddens litmus stronger than before. This surprising appearance is explicable in the following manner: The acid phosphate of sodium present in the urine decomposes the urea on the application of heat, and ammonio-sodic phosphate is formed. But this salt has the property of giving up its ammonia at a temperature of  $100^{\circ}$ , and changing again to acid phosphate of sodium; the acid phosphate of sodium, therefore, acts destructively on the urea as long as the evaporation lasts, and the urine can, therefore, always retain its acid reaction while a large amount of ammonia is in the distillate.

With some care, however, it is possible to detect with the greatest certainty small amounts of ammonium salts in normal urine, and the labors of Heintz, Boussingault, and myself remove all doubt on this point.

O. Schultzen and L. Riess found trimethylamin also in the urine in acute atrophy of the liver.

C. M. Tidy and W. B. Woodmann\* have carried out thorough investigations with regard to the amount of ammonia in the urine in health and disease. These authors give as the normal average 0.162 gram of  $\text{NH}_3$  in twenty-four hours. They observed a diminution to one-half in acute articular rheumatism, in albuminuria, phthisis, and nervous diseases. The normal amount of ammonia sank to one-quarter in erysipelas, variola, typhus and typhoid fevers. It was in normal amount in cancer, heart diseases, and chronic alcoholism, and was increased in

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\* Proc. of Royal Soc. XX., p. 362.



diabetes and gout. It is said to almost wholly disappear from the urine shortly before death. In two hundred cases examined it was only twice wanting in the urine.

Hilger found\* a very considerable increase of ammonia after taking asparagus for a long time; here it is evidently produced by the decomposition of the asparagin.

*Detection.* To detect ammonium salts in acid urine, freshly-passed normal urine is precipitated with a mixture of acetate and subacetate of lead, filtered, and the filtrate, while cold, treated with milk of lime in a flask. The flask is closed with a stopper on which a piece of moistened turmeric paper is fastened, when the brown color can be very quickly perceived. Now where does the ammonia, set free by milk of lime in the cold, come from? Urea is not decomposed by milk of lime in the cold, and the coloring and extractive matters are removed by oxide of lead. *As no substance is discovered in normal urine which is precipitated by the acetate and subacetate of lead, and is decomposed by milk of lime in the cold in a few seconds with the development of ammonia; we must consider the presence of ammonium salts in normal freshly-passed urine as established.*

For my quantitative estimations I used a method given by Schlössing, which depends on the fact that an aqueous solution containing free ammonia, when exposed to the air at ordinary temperatures, allows its ammonia to evaporate in a relatively short time, when it is contained in as flat a vessel as possible in not too deep a layer. The ammonia which escapes is made to combine with a standard sulphuric-acid solution and is determined volumetrically. (See Part Second for description of the process.)

After I had convinced myself of the usefulness and reliability of the method,† I commenced the determination of the amount of ammonia which is passed by a healthy man in twenty-four hours. My experiments showed that in twenty-four hours, on an average, 0.7243 gram of ammonia were secreted by a man from twenty to thirty-six years of age, which corresponds to 2.2783 grams of chloride of ammonium. The amount varied in twenty-four experiments between 0.3125 and 1.2096 gram of

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\* Erlanger Sitzungsberichte, 1873.

† Journ. f. pract. Chemie, Band 64, p. 177.



ammonia, corresponding to 1.4272 and 3.8038 grams of chloride of ammonium. I started my experiments with two healthy men of twenty and thirty-six years respectively, and found that a somewhat greater amount of ammonia was passed in twenty-four hours by the latter on the average. The following summary will serve to show the difference :

	Man of 20 years.		Man of 36 years.		Difference.	
	NH <sub>3</sub>	NH <sub>4</sub> Cl.	NH <sub>3</sub>	NH <sub>4</sub> Cl.	NH <sub>3</sub>	NH <sub>4</sub> Cl.
In twenty-four hours,	0.6137	1.9305	0.8351	2.6361	0.2214	0.7065
In 1,000 cc. of urine,	0.3939	1.2390	0.5245	1.6560	0.1306	0.4170

Chloride of ammonium, taken into the economy, passes out in part unchanged by the urine.

## § 20. SILICIC ACID.

Silicic acid occurs only in very small amount in the urine. To obtain it the following method is adopted: An amount of urine, not too small, is evaporated in a platinum or silver evaporating dish and ignited. The ash obtained is mixed with an excess of a mixture of chemically pure carbonate of sodium and potassium, and fused for a time in a platinum crucible. The mass is dissolved in water, rendered acid with hydrochloric acid, and evaporated to dryness in a platinum dish on the water bath. The dry residue is extracted with hydrochloric acid and water, and pure silicic acid remains behind.

The silicic acid thus obtained is white, pulverulent, without taste or odor, and grits between the teeth. It is soluble neither in water nor in acids, but boiled with a solution of carbonate of sodium it is taken up entirely without leaving any residue. (Tests of purity.)

## § 21. NITRATES AND NITRITES.

According to the investigations of Schönbein, every normal urine contains small amounts of nitrates, which without doubt come from the food taken, since all spring and river water, as well as many vegetables, cabbage, spinach, salad, etc., contain small amounts of nitrates. The nitrates are gradually reduced to nitrites by the urinary fermentation which soon takes place

on standing, and they appear to suffer a further decomposition in the later stages of fermentation. The following are to be mentioned as delicate reagents for nitrous acid :

1. A deep blue color is produced by the slightest amount of nitrites with a paste of starch and iodide of potassium feebly acidified with dilute sulphuric acid.

2. An acidulated solution of pyrogallie acid is colored deep blue by nitrites with the evolution of nitric oxide gas. If the test is performed in a flask, the nitric oxide gas on contact with the air becomes nitric peroxide, which turns a strip of paper moistened with starch and iodide of potassium paste, and hung in the flask, blue, and decolorizes indigo paper.

As long as the urine is completely clear, it never shows the reactions given for nitrous acid ; if, however, a cloudiness appears, due to commencing fermentation, the formation of nitrous acid immediately takes place, and the urine now shows an evident reaction with sulphuric acid and iodide of potassium, and starch paste. Also an indigo solution acidulated with hydrochloric acid and then completely decolorized by adding a few drops of potassic pentasulphide (Mehrfachschwefelkalium) is made blue again directly by such a urine. (Preparation of this reagent, see § 22, 2.) After long standing (eight to ten days) it shows these reactions in a greater degree, and finally gradually loses this power again wholly. If the urine is in that condition in which it blues the acidified iodide of potassium and starch paste most powerfully, it also gives the above-mentioned reaction with pyrogallie acid, etc.

It is easy to determine that fresh urine contains nitrates, according to Schönbein, if it is treated with potassium hydrate, and evaporated. Sulphuric acid sets free from the residue fumes which deeply blue the iodide of potassium and starch paste, and bleach indigo paper. The sulphuric acid here in the presence of alkaline chlorides sets free from the nitrates chlorine and hyponitric acid, which give rise to the reactions cited.

## § 22. HYDROGEN PEROXIDE.

This curious body was also first detected in the urine by Schönbein. The following reactions serve for its recognition :

1. Hydrogen peroxide bleaches a dilute tincture of indigo

only very slowly, but if only a few drops of a dilute solution of ferrous sulphate are added, the mixture becomes completely freed from its color in a short time.

2. If water is colored blue with tincture of indigo, so as to be non-transparent, treated with a little hydrochloric acid and then a few drops of a solution of potassic pentasulphide (Mehrfachschwefelkalium) added with stirring, the mixture becomes completely free from its blue color. If in the preparation of this reagent no more sulphuret of potassium was added than was just enough to decolorize the indigo tincture, the colorless and clear filtrate will be distinctly and immediately blued by water, which contains only traces of hydrogen peroxide, when a few drops of a dilute solution of ferrous sulphate are added to the mixture. By an excess of hydrogen peroxide, however, the blue color is made to disappear again. (Reaction 1.)

3. Hydrogen peroxide in the presence of ferrous sulphate immediately blues iodide of potassium and starch paste. This extraordinarily delicate reaction cannot be used, however, in urine, since every urine is able to form compounds with considerable quantities of free iodine, and consequently the blue color cannot occur.

*Detection in Urine.* To about 200 cc. of freshly passed urine a solution of indigo is added, drop by drop, until the mixture shows a distinct green color, it is then divided into two equal parts. If fifteen or twenty drops of a dilute solution of ferrous sulphate are added to one half, the color will soon appear to be of a lighter green or brownish yellow, a change of color which evidently comes from a partial or total destruction of the indigo tincture, while, on the contrary, the half free from iron continues to show its original green color. If, further, eight or ten drops of indigo tincture decolorized exactly by sulphuretted hydrogen (reagent 2) are allowed to drop into thirty or forty cc. of fresh urine, the mixture will not become colored blue at first, but only after adding a few drops of solution of ferrous sulphate. Sulphurous acid, which quickly reduces hydrogen peroxide, added to the urine in correspondingly small amount, hinders both reactions.

## III. ABNORMAL CONSTITUENTS OF URINE.

## § 23. ALBUMEN.

*(Serum Albumen.)*

		Scherer.	Mulder.
Formula unknown.	Carbon	54·883	53·5
	Hydrogen	7·035	7·0
	Nitrogen	15·675	15·5
	Oxygen	22·365	22·0
	Sulphur		1·6
	Phosphorus		0·4
		<hr/> 99·958	<hr/> 100·0

**A. Presence.** It is well known that albumen is the most important substance which the animal body requires for its preservation; it furnishes the material for its nourishment, as well as for the renewal of wornout organs. Its diffusion, therefore, in the whole body is large; it forms the chief constituent of the blood, the lymph, the chyle, all the serous fluids, and the liquids of the cellular tissue. In the normal condition albumen does not occur in the urine, but it occurs so frequently under pathological conditions, that it is necessary to test for it in every specimen whose composition we wish to ascertain. It occurs most frequently in all affections of the kidneys which are embraced under the name of Bright's disease.

W. Leube\* found albumen in the sweat at different times. Waldenström† repeatedly observed urine containing albumen, both after the external and internal use of carbolic acid.

**B. Preparation of Pure Albumen.** Blood serum is treated with very dilute acetic acid, drop by drop, till a flocculent precipitate just forms, it is filtered, the filtrate evaporated in a vacuum, or on a water bath, at 40° C., to a small volume, nearly saturated with carbonate of sodium, and the residue subjected to dialysis. If, after frequent renewal of the external water, no more salts pass through the dialyser, the contents of the cell is evaporated in a vacuum again, or on a water bath at 40°, to dry-

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\* Virchow's Archiv, Band 48, p. 181.

† Neues Jahrbuch d. Pharm., Band 84, p. 111.

ness. Albumen, thus prepared, is not yet wholly free from salts. (Hoppe-Seyler.)

C. *Chemical Properties.* Purified serum albumen is, in the dry state, a yellow, vitreous, translucent mass, which dissolves in water to form a viscid fluid.

1. A solution of serum albumen, with which the albumen occurring in urine is identical, has, in neutral aqueous solution, a specific rotation of the plane of polarization of  $-56^{\circ}$  for the line D of the solar spectrum.

2. Alcohol causes a precipitate in solutions of albumen, which, partly at least, dissolves in water again, if the alcohol is removed immediately. By the prolonged action of alcohol all of the serum albumen appears to be coagulated.

3. If a solution of albumen is treated with acetic acid until it has a strong acid reaction, and then a few drops of ferrocyanide of potassium solution are added, a white, flocculent precipitate is produced. (Quantitative volumetric estimation by the method of Bödeker.)

4. If albumen is heated with concentrated hydrochloric acid, or better, after the addition of a little sulphuric acid, a violet fluid results.

5. Concentrated nitric acid colors a fluid containing albumen yellow, after the application of heat (xanthoproteic acid). After the addition of sodic hydrate, the yellow color of the solution becomes orange red.

6. If a solution of albumen is warmed in a test tube over a spirit lamp, it commences to become turbid soon after the temperature has reached  $60^{\circ}$  or  $65^{\circ}$ ; it is observed that the cloudiness commences to be visible first at the surface of the fluid, and gradually spreads through the whole. Soon a flocculent, white, or, under certain circumstances, more or less colored coagulum occurs, since albumen at  $72^{\circ}$  or  $73^{\circ}$  C. changes to the insoluble form. There are, however, several things to be observed in this simple reaction: if the albumen is very dilute, the cloudiness often occurs only after boiling the fluid, from which, at times, distinct flakes separate, especially after prolonged boiling or standing. If the reaction of the fluid is feebly acid, a complete coagulation results in most cases, if the acid is not in excess; if the solution has a neutral or alkaline reaction, only a slight cloudiness follows on heating, even

when the amount of albumen is considerable; it remains in solution combined with potassium. If, however, before heating, as much acetic acid is added as is necessary to saturate the alkali, the separation takes place completely in the form of coarse flakes. An excess of acid, however, is to be carefully avoided, since otherwise the albumen remains more or less dissolved by the acetic acid, even on boiling.

Chloride of sodium and other neutral salts of the alkalies lower the temperature at which a solution of albumen coagulates, therefore this takes place in acid urine usually below 70° C.

7. If a solution of albumen is treated with acetic acid until it has a strong acid reaction, and an equal volume of a saturated solution of sulphate of sodium is added to the fluid, and then heated to boiling, complete coagulation results.

8. A solution of mercury prepared by dissolving the metal, first in the cold and then with moderate heat, in its own weight of strong nitric acid, of specific gravity 1.41 (boiling point 115° to 120° C.), diluting with two volumes of water, and after standing a while decanting from the crystalline precipitate, forms the most delicate reagent for albumen, as well as for all protein bodies, whether dissolved or undissolved. If we heat a fluid containing albumen with this mercury solution to from 60° to 100° C., an intense red color is obtained, which disappears neither in the air nor on prolonged boiling.

Millon's reagent can, according to Vintschgau and Gintl,\* be prepared as follows: a little nitrite of potassium is added to a solution of mercuric nitrate and the necessary amount of nitric acid added only when the reaction is performed.

9. Dilute nitric acid added in not too small amount gives in solutions of albumen a white precipitate of nitrate of albumen which is soluble in an excess of nitric acid and an excess of water.

(Important reaction.) Other mineral acids behave in the same manner.

10. Most metallic salts, as alum, cause precipitates of varying composition. The precipitate produced by mercuric chloride (corrosive sublimate) is especially important.

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\* Chem. Centralbl., 1869, p. 860.

11. Sugar and concentrated sulphuric acid produce a beautiful red color with all protein bodies, just as with the biliary acids. (See Biliary Acids.) (Schultze.)

12. Albuminoid bodies treated with a solution of sulphate of copper and then warmed after the addition of hydrate of potassium or sodium, give the solution a beautiful violet color. This reaction does not appear or only incompletely when the alkali is added before the copper salt.

13. Solid albumen on being treated with sulphuric acid containing molybdic acid becomes colored a beautiful dark blue. (Fröhde.)\*

Albumen reacts to most of the above tests in common with the other protein substances.

14. All albuminates, the peptones and unformed ferments not excepted, when dissolved in excess of glacial acetic acid, give after the addition of concentrated sulphuric acid beautiful violet-colored solutions, which have a feeble fluorescence. When properly concentrated these fluids produce in the spectrum an absorption band which, like that of urobilin and cholelithin, lies between the lines b and F. (A. Adamkiewicz.)

D. *Preparation of Albumen Absolutely Free from Salts by Diffusion.* B. Aronstein† obtained by the dialysis of an alkaline or neutral solution of albumen, by making use of the finest English parchment paper, and continuing the process three or four days at a temperature of  $+10^{\circ}$  to  $12^{\circ}$  C., during which the external water was changed two to three times, an albumen which on being ignited left no trace of ash behind.

The chief properties of this pure preparation are as follows:

1. Albumen is a body completely soluble in water, and neither the soluble nor the insoluble salts in the animal fluids aid in retaining it in solution.

2. Pure albumen is coagulated neither by a boiling temperature nor by alcohol; the coagulation which is thus produced is caused only by the salts in its natural solutions.

3. There is no compound of albumen with the insoluble salts of the animal fluids, to which these salts owe their solubility in the latter; they are kept in solution rather by means of an

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\* Zeitschrift f. analyt. Chem., Band 7, p. 266.

† Archiv für Physiologie, Band 8, p. 75.



organic substance contained in blood serum, as well as in the albumen of eggs, and which does not belong to the class of albuminoid bodies.

4. Blood serum, like egg albumen, contains, besides the albumen, another albuminoid body, paraglobulin, dissolved by the crystalloid constituents.

*E. Detection.* The recognition of albumen in urine depends on very simple tests, which, carried out with care, allow of an accurate conclusion. In the first place the reaction of the clear or previously filtered urine is determined, a small test tube is then about half filled and heated over the spirit lamp. If the urine has an acid reaction and albumen is present, as soon as the temperature has reached  $50^{\circ}$  or  $60^{\circ}$  C. a cloudiness will make its appearance at the surface of the fluid, which is soon followed by a coagulation of the albumen. If, however, the urine is neutral or alkaline, for the reason given above, the precipitation does not take place, but for the most part only a milky turbidity. But if in this case the boiled urine is treated with nitric acid until it has a strong acid reaction, a permanent precipitate takes place, when albumen is present. But it is to be remarked that the nitric acid must be added in considerable excess, since albuminoid bodies may remain in solution when too little is added.

Nitric acid has many advantages here over acetic acid, which has been heretofore used for rendering urine acid, since, in the first place, the addition of acetic acid must be made with great care, for an excess completely stops the separation of albumen, and, in the second place, acetic acid, according to the investigations of Reissner, causes, in a urine which contains dissolved mucus (mucin), a similar turbidity insoluble in an excess of acetic acid, which may readily be mistaken for a separation of albumen.

For further confirmation of the presence of albumen the reactions 3 and 7 are of especial service.

Cases may occur, however, where a precipitate forms on boiling the urine, especially when it is only feebly acid or neutral, even when no trace of albumen is present. This precipitate consists of the earthy phosphates which are held in solution in feebly acid urines mostly only by free carbonic acid, after the expulsion of which by heat they are precipitated in flocculi, and



in this form can scarcely be distinguished from coagulated albumen by the naked eye. The doubt is readily removed if, after cooling, nitric acid is added to the fluid in which the precipitate is suspended, and the mixture shaken; if the precipitate consists of phosphates they will dissolve and the fluid become clear; if, however, it is albumen, it will not disappear. This frequently happens, so that the subsequent test with nitric acid, especially when the cloudiness which occurred on heating was but small, must never be omitted.

If, moreover, the urine contains resinous matters, as, according to Maly's investigations, may be the case after the internal use of turpentine, balsam copaiba, etc., a whitish-yellow cloudiness, not unlike precipitated albumen, occurs after the addition of hydrochloric or nitric acid, which immediately disappears, however, after the addition of alcohol, and thus may be easily distinguished from albumen.

The test with nitric acid can also be performed in the following very neat manner, according to Heller. A test tube is filled about half an inch high with pure concentrated nitric acid, and a layer of the clear urine to be tested is poured carefully down the side of the tube by means of a pipette, so as to cover the acid. If the manipulation is well performed the urine floats on the nitric acid, and the mixture of the two takes place gradually. At the point of contact there is formed almost always an intense red, violet or blue ring, the indican reaction. Care must be taken not to confound this play of colors with the reaction of the biliary coloring matters, unless a green color can be distinctly recognized under the blue. If the urine contains albumen, a cloudy zone, sharply bordered above and below, forms on applying this test at the point of contact of the two fluids, which zone can be recognized with great distinctness even when only traces of albumen are present. The reaction lasts quite a while, but after a long time the coagulated albumen gradually sinks to the bottom. A turbidity, similar at first sight, may also occur when the urine contains an abundance of urates; a cloudy zone also forms in this case, but it stands at a higher level than the albumen zone. The lower edge, also sharply defined, stands above the point of contact of the two fluids, usually higher even than the upper border of the albumen zone; it is, moreover, not sharply bordered above, but diffused and

rising toward the surface of the urine. If the urine contains albumen, and at the same time a large amount of urates, two zones may form, a lower one of albumen, which is separated from the upper one of urates by a clear layer. It is better, however, in such a case to dilute the urine with two or three parts of water before testing it, in order to prevent the urate reaction, or at least to reduce it to a minimum. Turbidity from urates, moreover, disappears on the application of gentle heat, and all doubt can thus be removed readily. A precipitate of nitrate of urea may also take place in very concentrated urines, but this is crystalline and disappears immediately on the addition of water.

Méhu \* uses for testing for albumen, qualitatively, a mixture of equal parts of crystallized carbolic acid and commercial acetic acid, with two parts of 90 per cent. alcohol. Two or three per cent. of nitric acid and about ten per cent. of this carbolic acid solution are added to the urine, the mixture is shaken, and allowed to settle. The deposit takes place more quickly if, instead of nitric acid, one-half of its volume of a saturated solution of sulphate of sodium is used. This is a delicate reaction and very minute traces of albumen may be detected with certainty.

### SUPPLEMENT.

#### § 24. FIBRINE, CASEIN, ALBUMINOSE, PARALBUMEN, PARAGLOBULIN, PEPTONE, NEPHROZYMOSE.

1. *Fibrine*. Of the above protein substances, fibrine sometimes occurs in the urine. It separates in somewhat large masses, especially in cases of severe inflammation of the kidneys and urinary passages. Such a urine always contains blood also, and, as a result of this, albumen. Ackermann found fibrine in the urine in galacturia. I shall speak under the head of sediments of the peculiar tube-like urinary casts, which Frerichs regards as flattened coagula of fibrine.

Isolated cases have been observed, also, in which fibrine separated from the urine partly as a gelatinous mass, and partly as granular or fibrillated clumps.

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\* Zeitschrift f. analyt. Chem., Band 8, p. 522.

2. *Casein*. Casein has not yet been detected with certainty in the urine.

There are, moreover, at times protein substances, which appear in urine, which do not correspond in their characteristics to the ordinary ones. Thus Bence Jones describes a case \* in which he found in the urine of a man suffering from "softening of the bones," together with casts a peculiar albuminous substance which was characterized by being soluble in boiling water, precipitated by nitric acid, and dissolved on heating, but again separated on cooling. By its behavior with the reagents spoken of above under albumen, as acetic acid, ferrocyanide of potassium, etc., it was proved to be, without doubt, a protein substance; but we cannot regard it as albumen or casein on account of its anomalous behavior with water and nitric acid, at least not until we have succeeded in converting albumen or casein artificially into these peculiar modifications.

3. *Albuminose*. Baylon describes an albuminoid substance under the name of albuminose, which is said to occur also in normal urine. According to Mialhe this substance has the same relation to albumen that glucose has to starch (?). Albuminose is not precipitated by heat, acids, or alkalies, it is precipitated by tannin and many metallic salts. It is said, as already remarked, to occur in every normal urine as well as in pathological cases. In a urine of Bright's disease, however, where there was much albumen, no albuminose could be found. Baylon designated cupric tartrate as a very delicate reagent for albuminose. After the addition of a few drops of potassic hydrate the urine is boiled, filtered, and then a solution of cupric tartrate added, until the mixture has a faint blue color. After one or two hours tartrate of albuminose (?) precipitates, which dissolves on heating, but separates again on cooling.†

C. Gerhardt ‡ states that different varieties of albumen occur in the urine of patients suffering from kidney disease. In several cases the urine was precipitated neither by boiling nor by the addition of nitric acid, but alcohol separated substances which gave decided reactions for albumen.

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\* Annal. d. Chem. u. Pharm., Band 67, p. 97 to 105.

† Canstatt's Jahresbericht, 1860, p. 270.

‡ Centralblatt f. d. med. Wissenschaft, 1869, p. 174.

4. *Paralbumen and Paraglobulin.* E. Masing \* also describes a case of Bright's disease in which the urine, together with serum albumen, contained much paralbumen. This urine gave immediately, after the addition of water, a milky cloudiness, which disappeared on being treated with acids, alkalies, and also with a solution of common salt.

Edelfsen† made the same observation in thirty-one cases of albuminuria. The cloudiness of the urine, on dilution with water, first occurred after a few minutes, and was for the most part increased by the introduction of carbonic acid. Edelfsen considers this albuminoid body, as well as the paralbumen found by Masing, to be paraglobulin, although he did not succeed in causing the coagulation of fluid containing fibrinogenous substance by means of it when precipitated.

*Detection of Paraglobulin in Albuminous Urine.* The urine, after filtration, is diluted with water till its specific gravity sinks to 1,003 or 1,002, so that its amount of solid constituents is excessively small. Under certain circumstances, the dilution alone may give rise to the separation of paraglobulin, at least Edelfsen observed‡ a cloudiness frequently as soon as he had diluted the albuminous urine with water, in the proportion of 1:20. If now carbonic acid is conducted through the dilute fluid, for from two to four hours, almost all albuminous urines give turbidities of paraglobulin, which often, after from twenty-four to forty-eight hours, settle as distinct precipitates. (H. Senator.)§

The precipitate thus obtained is milk white, of a fine, flocculent character, and dissolves completely on the addition of a one per cent. hydrochloric acid solution, also of a few drops of a solution of common salt, and likewise in concentrated acetic acid. It separates so completely from the solution of salt, on heating, that no trace of an albuminous body is any longer demonstrable in the filtrate. The flakes separated on heating do not dissolve again in acetic acid, at least if added in moderate amount. If the precipitate is dissolved in a trace of sodic hydrate, filtered, and treated with clear pericardial or perito-

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\* Beiträge zu Albuminometrie, Dorpat, 1867, bei H. Laakmann.

† Centralblatt f. h. med. Wissenschaft, 1870, p. 367.

‡ Deutsch. Archiv. f. klin. Med., Band 7, p. 69.

§ Virchow's Archiv, Band 60, p. 476.

neal fluid, a turbidity occurs on shaking, which, after prolonged standing, is followed by a copious flocculent precipitate.

According to Senator, paraglobulin can be detected in every urine which contains coagulable albumen. Of the chronic kidney diseases, amyloid degeneration appears to yield the urine which is relatively richest in paraglobulin. Alkali albuminate, or a body which is obtained from the blood serum after precipitation of the paraglobulin by acetic acid, does not appear to occur in the urine at all, or only in slight traces.

5. *Peptone*. Peptone-like bodies were found by O. Schultzen and L. Riess\* in the urine, after phosphorus poisoning. These, by precipitating from the strongly concentrated urine by alcohol, redissolving in water, and reprecipitating with alcohol, were obtained free from all coloring matters. The identity of this peptone-like substance with the true albumen peptones is still doubtful.

*Detection of Peptone in Albuminous Urines.* The albumen is removed from albuminous urines by heat, with or without the addition of acetic acid, by the familiar method, and the filtrate mixed with three times its volume of alcohol by shaking. The precipitate which takes place, dissolved in water after washing with alcohol, is colored yellow on heating with nitric acid, and, in short, shows all the reactions of an albuminous body.

Gerhardt† observed peptone frequently in urine which was free from albumen; he found it sometimes as a forerunner, and sometimes as a follower of ordinary albuminuria.

Senator‡ was able to detect peptone in every albuminous urine in small amount.

6. *Nephrozymose*. Finally, according to Bechamp, a protein substance can be precipitated from every normal urine by three times its amount of 88 to 90 per cent. alcohol, which, after washing, is soluble in water; it is capable of changing starch into sugar at 60° to 70° C., and Bechamp has given it the name of nephrozymose.

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\* *Annalen des Charité Krankenhauses zu Berlin*, Band 15, p. 9, etc.

† *Wiener med. Presse*, 1871, p. 1.

‡ *Loc. cit.*, p. 488.

## § 25. URINARY SUGAR. GRAPE SUGAR.

Anhydrous : Carbon	40·00	Crystallized :	36·36
Hydrogen	6·66		7·07
Oxygen	53·34		56·57
	<hr/>		<hr/>
	100·00		100·00

Formula :  $C_6H_{12}O_6$  [ $C_{12}H_{22}O_{11}$ ]  $C_6H_{12}O_6 + H_2O$  [ $C_{12}H_{22}O_{11} + 2aq.$ ].

A. *Presence.* Grape sugar, which is perfectly identical with urinary sugar, is found, as is well known, very wide-spread in the vegetable kingdom. But it also occurs in the animal kingdom, partly normally, partly in disease in various fluids.

Grape sugar always exists in the contents of the small intestine, and in the chyle, after taking food containing sugar or starch ; it is found in the hen's egg—both in those in the process of hatching and in those not being hatched, in the yolk as well as in the white—in the amniotic and allantois fluids of cows, sheep, and swine, and in the liver. Bernard also finds it constantly in the blood, especially in the hepatic vein ; the blood of the portal vein, on the contrary, contains no sugar, so that its formation must occur in the parenchyma of the liver.

According to the most recent and comprehensive investigations of Seegen,\* there appears to be no doubt whatever that the excretion of sugar by the urine is not a physiological function, and that normal urine, contrary to the assertions of Brücke and Bence Jones, contains no sugar. Sugar occurs in large amount only in diabetes mellitus, but it is then increased in the blood, the vomitus, the saliva, the sweat, etc. Sugar has also been found in the urine, at times, in other diseases ; it appears to occur especially in disturbances of the abdominal circulation. By wounding certain points of the medulla oblongata in animals sugar may be made to appear temporarily in the urine. According to Lehmann sugar appears in the urine of women from twenty-four to forty-eight hours after weaning an infant. These observations of Lehmann correspond to the assertions of De Sinety,† according to whom, whenever there is an obstruc-

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\* Seegen, *Der Diabetes Mellitus*, 2 Aufl., p. 196.

† *Gazette med. de Paris*, 1873, p. 573.

tion to the flow from the lacteal gland, sugar appears in the urine. If, on the contrary, the production and discharge of milk retains its equilibrium, sugar disappears from the urine, and the latter becomes normal. Wollert and Almén\* observed the occurrence of sugar in the urine after the internal use of oil of turpentine.

According to the investigations of A. Ewald,† subcutaneous injections of nitrobenzol and nitrotoluol give rise to saccharine urine in rabbits. In dogs, however, it was seen only when nitrobenzol was given in large doses internally (0·8 to 3 grams). F. A. Hoffmann‡ also observed a large amount of sugar in the urine in rabbits after the injection of 0·2 to 0·6 gram of nitrite of amyl.

*B. Microscopic Properties.* Diabetic sugar crystallizes in irregular masses, which appear as warty conglomerations, and consist of cauliflower-like groups of laminæ. These laminæ have a rhombic shape. If the crystallization takes place rapidly it does not appear in laminæ even when seen under the microscope, but in irregular, striated roundish masses.

*C. Preparation of Chemically Pure Grape Sugar.*—1. If pure cane sugar is dissolved in 80 per cent. alcohol, to which a little hydrochloric acid has been added, with frequent shaking until it is saturated, after long standing chemically pure grape sugar separates in white crystalline crusts. (H. Schwarz.) After a long time, when no further separation follows, the crystals are collected, thoroughly washed with alcohol, dried in a dessicator, and finally recrystallized from boiling absolute alcohol.

2. The best starch sugar is dissolved on the water bath in about half its weight of water, and then filtered into a glass funnel whose orifice is closed with a stopper. When the funnel is nearly filled it is covered with a glass plate and put on a stand in a cool place for several months, when the grape sugar crystallizes out as hydrate.

The mother liquor is allowed to flow away, the sugar is covered with a layer of 80 per cent. alcohol, and treated with it until the sugar is dazzlingly white. Then it is dried, first in the open air, and finally in a dessicator over chloride of calcium.

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\* Neues Jahrb. d. Pharm., Band 84, p. 163.

† Centralblatt f. d. med. Wissenschaft., 1873, No. 52.

‡ Archiv für Anatom. u. Physiologie. 1872, p. 746.



Heat is to be applied only when most of the moisture is removed, because otherwise the sugar is softened by the moisture and cakes together. (Mohr.)

D. *Chemical Properties.* Pure grape sugar is white, odorless, by no means as sweet as cane sugar, and is also less soluble in water. Its solution has no reaction on vegetable colors, and turns polarized light to the right. It is quite soluble in alcohol, not at all so in ether. If crystallized grape sugar is exposed for a long time to a temperature of  $100^{\circ}\text{C}$ ., it loses its water of crystallization.

2. The specific rotation of an aqueous solution of grape sugar, if the solution has been heated or has stood a long time, is  $+56.4$  for yellow light. A freshly prepared cold solution causes a greater rotation to the right of the plane of polarization when tested immediately after dissolving it, but on long standing, and more quickly if heated, it sinks to  $+56.4$ .\*

3. In contact with bodies containing nitrogen, especially casein, it undergoes lactic acid and, later, butyric acid fermentation. In diabetic urine it changes into an acid even at medium temperatures, more quickly at a temperature of from  $25^{\circ}$  to  $40^{\circ}\text{C}$ ., which, according to circumstances, may be acetic, butyric, or even lactic acid.

4. Grape sugar forms with several bases peculiar compounds called saccharates.

a. *Saccharate of Potassium*,  $\text{K}_2\text{O} + \text{C}_6\text{H}_{12}\text{O}_6$  [ $2\text{KO} + \text{C}_{12}\text{H}_{22}\text{O}_{12}$ ], is readily obtained if an alcoholic solution of sugar is mixed with a solution of caustic potash in alcohol. The compound precipitates immediately in white flakes, which stick together when exposed to the air, deliquesce, and attract carbonic acid.

b. *Saccharate of Calcium*. If a solution of sugar is treated with an excess of quicklime, the solution filtered and the filtrate treated with alcohol, this compound separates as a white mass.

c. *Compound of Grape Sugar with Chloride of Sodium*,  $\text{NaCl}$ ,  $2(\text{C}_6\text{H}_{12}\text{O}_6) + \text{H}_2\text{O}$  [ $\text{NaCl}, 2\text{C}_{12}\text{H}_{22}\text{O}_{12} + 2\text{HO}$ ]. If a solution of grape sugar is mixed with a solution of chloride of sodium, and the mixture left to spontaneous evaporation in the air, the compound crystallizes in large, colorless, six-sided double pyramids or rhombohedra. The crystals are hard, readily pulverizable,

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\* Zeitschrift f. analyt. Chem., Band 14, Heft 3 u. 4.



easily soluble in water, and difficultly so in alcohol. They contain 13.52 per cent. of chloride of sodium.

5. If a solution of grape sugar is warmed with potassic or sodic hydrate, it becomes a beautiful brown-red color; if nitric acid is then added, a piercing, sweetish odor is evolved, which reminds one partly of caramel and partly of formic acid.

6. If a solution of indigo carmine, made alkaline with carbonate of sodium, is heated with a little grape sugar to boiling, it becomes colored, if only a small amount of sugar is added, first green then purple, and, with more sugar, red, and finally yellow. If the hot yellow solution is shaken, so that the oxygen of the air can act upon it, the play of colors is reversed. The mixture becomes colored purple red, then green, and finally blue again; yet on standing quietly the yellow color soon reappears. (Mulder.) This reaction is very brilliant, and allows very small amounts of sugar to be detected. With mere traces of sugar only a very weak blue indigo solution should be used.

7. If a solution of sugar is treated with a little caustic potash and a few drops of a solution of sulphate of copper, either no precipitate occurs, or that which takes place dissolves again to a beautiful blue fluid. If this mixture is heated, the fluid is first colored orange yellow, soon becomes cloudy, and finally a beautiful red precipitate of cupreous oxide separates. This reduction takes place after long standing in the cold without the application of heat. According to the investigations of Salkowski this reaction has two phases. First a bluish-green precipitate occurs, a compound of hydrated cupric oxide with sugar, which dissolves in an excess of sodic hydrate which soon decomposes it. An excess of sodic hydrate is absolutely necessary in the employment of the reaction. Uric acid, hypoxanthin, mucus, etc., likewise cause a reduction of cupric oxide when heated, while red cupreous oxide is separated. It is well, moreover, to bear in mind that many substances by their presence may hinder the separation of cupreous oxide, as, for example, albuminous matters, especially peptone, kreatin, kreatinin, pepsin, urinary coloring matter, etc.

8. If a solution of sugar is placed in a small flask with a little yeast, fermentation will soon occur, especially at a temperature of 15° to 20° C. Its progress can be very well observed in the following apparatus, fig. 2.

A is a small glass flask, in which the solution of sugar is brought in contact with the yeast; this flask is connected with a small flask, B, which is half filled with lime or baryta water by means of the glass tube, c. The tube, a, is closed at the top by a piece of wax, b. If the mixture, A, is heated to the above temperature, the solution of sugar will become cloudy after a short time; it commences to foam considerably, and bubbles of gas develop very regularly. This gas consists of carbonic anhydride, and, on going through the baryta or lime water, will render it cloudy by the separation of carbonate of barium or calcium, which will be precipitated. When the evolution of gas finally ceases, the fluid in A becomes clear, has lost its sweet taste, and instead has assumed a vinous one. The sugar is decomposed into alcohol and carbonic anhydride, during which decomposition, however, a few alcohols homologous to ethylalcohol are always formed in small amount, as well as traces of glycerine and succinic acid.

FIG. 2.

If the amount of sugar is small, a test tube is filled with mercury and inverted in a small mercury bath. By means of a pipette with a curved point, a little neutral or faintly acid solution of sugar treated with active well-washed yeast is allowed to rise in the tube, and is left at rest at a temperature best of 25° or 30° C. If, after one or two days, the development of gas is ended, a little concentrated potassic hydrate is allowed to rise up into the fluid by means of the pipette, and this will completely absorb the disengaged gas.

9. If a solution of grape sugar is treated with a weak ammoniacal solution of nitrate of silver, and is heated to boiling and kept for a time at this temperature, it deposits metallic silver in the form of a beautiful polished metallic mirror. This reduction can be of service under certain circumstances, since it is not prevented by the presence of ammonia. It is not to be forgotten, however, that many other matters, as, for example, tartaric acid, etc., reduce nitrate of silver in a similar manner.

10. If a solution of sugar is treated with an equal volume of carbonate of sodium solution (three parts of water and one of crystallized salt), a little subnitrate of bismuth added, and boiled awhile, the oxide of bismuth is reduced with a black color. The slightest blackening, or a gray coloration of the snow-white bismuth salt, shows the presence of urinary sugar in the most decided manner, since, according to Böttger, no other constituent of urine has a reducing action on that salt of bismuth. The urine must, however, be absolutely free from albumen; since otherwise black sulphide of bismuth is readily formed, which may give rise to erroneous conclusions.

The reaction is quite successful also with an alkaline solution of bismuth oxide, which is obtained by precipitating a solution of bismuth with a large excess of sodic hydrate, and adding drop by drop, with gentle heat, a solution of tartaric acid, until the precipitate which takes place is just dissolved again. According to Almén, four grams of Rochelle salt are dissolved in one hundred of potassic hydrate of specific gravity 1.33, gently warmed, and subnitrate of bismuth added as long as it dissolves; about two grams will be necessary.

11. If a solution of sugar containing hydrate of potassium is treated with a few drops of molybdate or tungstate of ammonium, heated to boiling, and then acidulated carefully with hydrochloric acid, there results a blue color of molybdate of molybdenum, or tungstate of tungsten. In hydrochloric acid solutions sugar reduces at the boiling temperature only the molybdic acid, with the formation of a blue color; yet this reaction is not nearly as delicate as in an alkaline solution. (Huizinga.)\*

E. *Detection.* The methods of detecting sugar in the urine are different, according to the amount supposed to be present. If the twenty-four hours' amount of urine is large (four to six liters), if the color is greenish yellow, and, at the same time, the specific gravity is high, at least above 1.020, it is probable that the urine to be tested is diabetic. In this case the detection of the sugar is simple, since diabetic urine, decolorized by animal charcoal, behaves very nearly like a pure solution of sugar with almost all reagents. If the urine in question is also

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\* Archiv d. Physiologie, Band 8, p. 496.

free from albumen, which must be ascertained according to § 23, the different tests for grape sugar can be directly employed; in other cases, however, it must be first freed from albumen, observing the precautions given in § 23. To prove the presence of sugar, we proceed as follows:

1. Fifteen or twenty drops of the urine to be tested, decolorized with animal charcoal, and diluted with 4 or 5 cc. of water, are treated with half a cc. of sodic or potassic hydrate, and then a very dilute solution of sulphate of copper is added drop by drop. If sugar is present, the precipitate first formed after shaking dissolves to a clear blue fluid. Too large an amount of the copper solution is to be avoided, especially if only small amounts of sugar are supposed to be present, since otherwise a black oxide of copper also separates on boiling, which conceals the red cupreous oxide which is formed at the same time. The clear blue solution is then heated nearly to boiling, without shaking, when a yellow cloud forms on the surface, and soon a precipitate of yellow or red cupreous oxide will follow without being heated further. The mixture of urine and potassic hydrate must not be heated before the addition of the solution of copper, since the sugar, especially if only a small amount is present, may be so changed that it no longer has a reducing action on the cupric oxide.

A second mixture, prepared in the same way, is allowed to stand quietly, without previous heating, from six to twenty-four hours. If sugar is present, there will be a precipitate of cupreous oxide in this case also. This control experiment is of great importance, and ought never to be omitted, since most of the substances which reduce the copper solution, like sugar, do so only when heated, or after prolonged boiling, and not like diabetic sugar in the cold.

If the amount of sugar is small, it is advisable to filter the urine beforehand through animal charcoal (four or five times) to completely decolorize it. The filtrate, which is clear as water, gives much better reactions than the original urine. (Maly, Seegen.)

Seegen \* has found, further, that pure animal charcoal retains considerable amounts of sugar. If, therefore, after complete

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\* Archiv d. Physiologie, Band 5, p. 375.

decolorization, the charcoal on the filter is washed with a little distilled water, it gives a very pure reaction. If the urine has a high specific gravity and a deep color, the reaction of the first washing from the charcoal is usually not so sensitive; but Seegen found that, in these cases, the second and third washings gave a much more characteristic reaction.

2. A second specimen of urine filtered, decolorized, and freed from albumen, is diluted with an equal volume of a solution of carbonate of sodium, a small amount of subnitrate of bismuth is added, and the mixture is heated to boiling for a long time. According to the amount of sugar present, a partial or complete reduction of the oxide of bismuth will follow, and, therefore, a gray or black color will occur. With small amounts of sugar, as little of the salt of bismuth as possible is to be taken, in order that a slight reduction shall not be concealed by a considerable excess of the white salt. If the specimen is then allowed to stand quietly, the undecomposed oxide of bismuth first settles, and then the reduced bismuth follows beautifully and distinctly in the form of a velvet-black ring. The reaction also succeeds very well with the alkaline solution of bismuth. (See Reaction 10.)

3. Another portion of the decolorized urine is placed in a tolerably long but narrow test tube, a little potassic hydrate is added, and the upper part of the column of fluid is heated to boiling. If sugar is present, this part will be colored yellow or brownish red, while the lower part retains its original color. In this manner the slightest changes of color may be distinctly perceived. This reaction is to be highly recommended as a confirmatory test.

The Reactions Nos. 6 and 9 give further confirmation, but especially the fermentation test, which may be undertaken in diabetic urine with the apparatus pictured in fig. 2.

Sugar may readily be obtained from diabetic urine, pure and in crystalline form. The following methods serve for this purpose:

I. A portion of urine is evaporated on the water bath to a syrupy consistence; the residue is allowed to stand, and, after a long time, the sugar will crystallize out in yellow warty masses. It is freed from urea and extractive matters by treating with absolute alcohol; the sugar is then extracted from the

residue by boiling spirit, and the solution allowed to evaporate. The sugar will remain behind tolerably pure, and can be readily freed from the alcohol which adheres to it by repeated recrystallization from water.

II. *Lehmann's Method.* An alcoholic solution is first prepared, by evaporating the urine and extracting with alcohol. This is evaporated to dryness, the residue dissolved in water, and the solution saturated with chloride of sodium. After evaporation, the chloride of sodium compound with sugar will crystallize, and may be obtained in pure crystals by repeated crystallization. They are dissolved in water, and precipitated carefully by sulphate of silver. The precipitate of chloride of silver is filtered off, and the filtrate evaporated to dryness; by extraction with alcohol the sugar is obtained chemically pure.

Without regard to the fact that these methods only succeed when the urine contains somewhat considerable quantities of sugar, yet cases occur in which the sugar is completely uncrystallizable, and differs from grape sugar by its power of turning polarized light to the left. In such cases, the residue of urine always remains syrupy and shows no trace of crystallization.

III. If the urine does not have the above characteristics, but still reduces the copper solution on being heated, without, however, separating cupreous oxide, but at most producing a yellow coloration of the mixture, it is necessary, in order to be able to prove the presence of sugar with certainty, to separate it in the purest possible form before the above reactions can be undertaken with a positive result. For example, a slight reduction of the copper solution can be caused by uric acid, etc., even when sugar is entirely absent. Even if a reduction should in fact be caused by sugar present, cupreous oxide may be held in solution by kreatinin, etc., wherefore this reaction loses all certainty. In this case there occurs at most a yellow coloration of the mixture without the characteristic precipitation of cupreous oxide. Such a solution on standing exposed to the air becomes colored blue again on the surface by oxidation. To avoid all of these uncertainties, any albumen present is first removed from a large amount of urine (500 to 800 cc.) according to § 23, the filtrate, or if no albumen is present, the original urine previously filtered, is evaporated on the water bath to a thick syrup, and allowed to stand in the cold from

four to six hours. Then after the residue has been divided as much as possible with powdered pumice-stone, it is extracted with ninety per cent. alcohol, with which, in not too small amount, the extract is allowed to remain in contact for at least some hours with frequent shaking. The clear filtered liquid is then treated with an alcoholic solution of pure potassic hydrate, until precipitation ceases, without, however, making use of too great an excess. If sugar is present, saccharate of potassium precipitates as a pitchy, sticky mass, always together with other compounds of potassium in a crystalline or flocculent form. When the potassium saccharate has settled, the spirit is quickly poured off from the precipitate, the latter is washed repeatedly with absolute alcohol, whether it is flocculent, crystalline, or pitchy, it is then dissolved in water, and the potassium quickly saturated with carbonic acid, in order to prevent a decomposition of the sugar. In most cases this solution gives the reactions already given, but since, under certain circumstances, substances are precipitated with the potassium compound which have a reducing action on cupric oxide, the presence of sugar is not yet placed beyond all doubt. According to Lehmann, therefore, the aqueous solution of the potassium precipitate, accurately neutralized with acetic acid, is precipitated with acetate of lead solution in moderate excess, filtered, the excess of oxide of lead removed by sulphuretted hydrogen, again filtered, and the fluid, usually clear as water, is evaporated on the water bath almost to dryness, so that at all events all of the sulphuretted hydrogen is removed. The residue is dissolved in water, and the tests given in I. are performed. If they are successful, the presence of sugar may be considered as proved, since it is difficult for any other substance to be contained in this fluid last obtained, which, like sugar, gives the reactions mentioned. In the copper test, if the mixture is allowed to stand in the cold, cupreous oxide will separate if sugar is present without the application of heat; moreover, only small amounts of the cupric oxide solution are to be taken, so that the mixture shows only a slight blue color. Finally the fermentation test yields the final decisive proof; this test can be carried out with great accuracy, even with very small amounts of sugar, in the apparatus described under Chemical Properties, No. 8. Fermentation occurs quickly in



the presence of sugar, and to prove that the gas is not derived from the decomposition of the yeast, it is expedient to perform a control experiment with yeast and pure water.

The alcohol formed by the fermentation can also be readily detected. For this purpose a few cc. of the fermented fluid are distilled, the distillate is treated with a few drops of a solution of iodine in iodide of potassium, potassic hydrate is added, drop by drop, until it is just decolorized, and the mixture is allowed to stand for a time. If alcohol is present, there soon, or after standing awhile, occurs a yellowish cloudiness of iodoform, which after complete settling is subjected to microscopic examination. Iodoform forms either regular six-sided tables very similar to cystin crystals or six-sided stars of great beauty. (Lieben.)\*

It must be remarked, however, that normal urine also, as Lieben has found, contains a volatile substance, which passes over on distillation and yields iodoform with iodine and hydrate of potassium. If we wish to subject the urine directly to fermentation with yeast, and to use the distillate for the iodoform reaction, the urine must first be evaporated to one-half its volume before adding the yeast, so as to remove this volatile substance.

In many cases where the original urine showed only very doubtful reactions for sugar, I have succeeded by this method in proving its presence with great distinctness by all of its reactions.

Leconte treated the potassium precipitate in the following manner: Tartaric acid in slight excess is added to its solution in as small an amount of water as possible, it is shaken, the tartrate of potassium is filtered off, and the cold filtrate treated with excess of carbonate of calcium till it has a perfectly neutral reaction. The filtrate is evaporated on the water bath, and the residue exhausted with absolute alcohol. This solution, after spontaneous evaporation, leaves behind, when sugar is present, a syrup, which after quite a long time, often only after months, deposits crystals which frequently fill the entire mass. If, however, one is content with the fermentation of the sugar instead of its extraction, according to Leconte the aqueous solu-

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\* *Annal. d. Chem. u. Pharm.*, Supplementbd. 7, p. 218.



tion of the potassium precipitate is treated with dilute sulphuric acid to saturation, the sulphate of potassium which separates after standing awhile is filtered off, a little water with yeast is added, and the mixture is put in the fermentation apparatus described.

To find sugar in normal urine Brücke uses the following methods, which are best mentioned here:

a. The urine (1,000 to 5,000 cc.) is first precipitated by a concentrated solution of sugar of lead, filtered, the filtrate treated with subacetate of lead till precipitation ceases, again filtered, and finally precipitated with ammonia. The last precipitate is collected on a filter, washed with water, and finally allowed to dry between thick layers of blotting paper which are renewed from time to time. The crumbled cake is first rubbed rather coarsely in a mortar with distilled water, and then a concentrated solution of oxalic acid is added with constant trituration, as long as a specimen filtered off continues to be rendered cloudy by further addition of oxalic acid. The filtrate is saturated with finely divided carbonate of calcium, again filtered, rendered feebly acid with acetic acid, evaporated to dryness, and the residue dissolved in a little water. Brücke performed the usual reactions with this solution as well as the fermentation test. Bence Jones does not decompose the lead precipitate by oxalic acid, as Brücke does, but in a simple way, after it has been suspended in water, by means of sulphuretted hydrogen. Bence Jones found in several normal urines (1,000 to 5,000 cc.) by this method small amounts of sugar (2 to 3 grains in 1,000 cc. of urine).

b. The urine is treated with strong alcohol till the mixture contains about four-fifths of absolute alcohol. It is well to take 200 cc. of urine, and mix it with 800 to 1,000 cc. of 94 per cent. alcohol. After it is mixed, a short time is allowed to elapse for the precipitate which has formed to settle, and then it is filtered into a beaker. An alcoholic solution of hydrate of potassium is then added, drop by drop, to the filtrate, with constant stirring, till a feeble though distinct alkaline reaction can be detected by litmus paper. The beaker is then allowed to stand twenty-four hours in a cool place, well covered up. The next day the fluid is carefully poured off, the beaker turned over on filter paper, so that the rest of the fluid may be ab-

sorbed, and then it is allowed to stand exposed to the air till the decided odor of alcohol can be no longer perceived. The bottom and, to a certain extent, the sides of the glass are covered with a crystalline coating, which is to be dissolved in as little water as possible, and this solution employed for the reactions given. But since under certain circumstances uric acid may exist in this crystalline deposit, it is well in any case to acidify the concentrated aqueous solution with hydrochloric acid, and leave it at rest for twenty-four hours, so that any uric acid present may separate. The neutral filtrate is then employed for the bismuth, copper, and potassium hydrate reactions, as well as for the fermentation test also when possible. The alcohol formed by fermentation is detected by the iodoform reaction, as given above, page 111, under III.

Bödecker first precipitates the potassium with tartaric acid from the concentrated aqueous solution of the crystalline deposit, removes the excess of the acid from the filtrate by carbonate of calcium, with which he allows the fluid to be in contact for a time, filters from the excess of tartrate and carbonate of calcium added, and uses the solution thus obtained for the copper, bismuth, and potassium hydrate reactions.

But Seegen,\* from his own investigations, considers that all the proofs of the occurrence of sugar in normal urine which Brücke and others advance are not sufficient, because the appearances which they give as sugar reactions can be produced in the same intensity by other substances also, which are not excluded by the processes employed.

The excretion of sugar by the urine is, according to Seegen, not a physiological function; according to him, normal urine contains no sugar.

The method recently given by Huizinga† for the detection of sugar in normal urine has not yielded me, on repeated trials, results which remove all doubt.

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\* Seegen, *Der Diabetes*, 2 Aufl., p. 224.

† *Archiv d. Physiolog.*, Band 8, p. 496.

## APPENDIX.

## § 26. ALKAPTON.

Bödecker \* found in the urine of a man forty-four years old, who suffered repeatedly from severe cough and expectoration after typhoid fever, a peculiar substance which had the property of absorbing large quantities of oxygen and becoming brown in the presence of an alkali. Bödecker calls this body alkapton. The patient at that time suffered great pain, which began from the sacrum, extended to the lower vertebræ, and thence radiated as lumbo-abdominal neuralgia. The amount of urine in twenty-four hours amounted to about 1,500 cc. (sp. gr.=1.020 to 1.025), and contained not over one per cent. of sugar. On the addition of potassic hydrate the reddish-yellow color of the urine became a dark brown from above downward, and a large amount of oxygen was absorbed, as Bödecker proved by a special experiment. A solution of copper was strongly reduced by the urine. Recently Fürbringer † detected alkapton by all of the tests given by Bödecker in the urine of a man twenty-nine years old, who suffered from lung disease. This urine contained no sugar.

## § 27. INOSITE.

Formula :	$C_6H_{12}O_6$	$[C_{12}H_{12}O_{12}]$	$\left\{ \begin{array}{ll} \text{Carbon} & 40.00 \\ \text{Hydrogen} & 6.66 \\ \text{Oxygen} & 53.34 \\ \hline & 100.00 \end{array} \right.$
Crystallized :	$C_6H_{12}O_6 + 2H_2O$	$[C_{12}H_{12}O_{12} + 4HO]$	

A. *Presence.* Inosite, until recently, was found only in the muscular tissue, but Cloëtta recently found this remarkable carbo-hydrate in the lungs (together with uric acid, taurin, and leucin), very abundantly in the kidneys (together with cystin and hypoxanthin), in the spleen (with uric acid, hypoxanthin, and leucin), and in the liver (with uric acid). Cloëtta and Neukomm were able to prove the presence of inosite with certainty in the urine of Bright's disease; on the other hand, it was not found in

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\* Annal. d. Chem. u. Pharm., Band 117, p. 98.

† Berliner klinische Wochenschrift, 1875, No. 24.

normal urine. W. Müller and Neukomm found inosite in the brain. Neukomm\* found it sometimes in considerable quantity in the kidneys as well as in diabetic urine, together with large amounts of sugar, while Vohl saw it occur gradually in a diabetic urine in the place of sugar. Valentiner was able to separate inosite in considerable quantity from the voluntary muscles of drunkards. Inosite is, however, a not unusual constituent of plants also; Vohl found it in unripe beans (*Phaseolus vulgaris*), W. Gintl† found it in the leaves of the ash, and Marmé states that he has found it in the juices of various plants. I found it myself in considerable quantity in the grape juice, in the leaf of the vine, in the must, and in wine.

B. *Microscopic Properties.* Inosite forms for the most part cauliflower-like groups of crystals, but at times it occurs in single crystals which are three or four lines in length. The crystals belong to the klinorhombic system. (Funke, Taf. VI., fig. 6; 2<sup>o</sup> Aufl., Taf. V., fig. 3.)

C. *Chemical Properties.* Inosite loses its water of crystallization in the air, and melts at 210° C. Its taste is distinctly sweet; it is easily soluble in water, and insoluble in ether and alcohol.

1. Melted inosite solidifies when rapidly cooled to pointed crystals; on slow cooling, on the other hand, it becomes a horny mass.

2. Inosite does not yield alcohol when treated with yeast, but in contact with putrefying cheese it yields lactic and butyric acids. The variety of lactic acid which is formed here is paralactic, which yields, on oxidation with chromate of potassium and sulphuric acid, malonic acid. (Hilger.)‡

3. If a solution of inosite is evaporated with nitric acid on platinum almost to dryness, and the residue is moistened with a little ammonia and solution of chloride of calcium, and the mixture is again evaporated carefully to dryness, a vivid rose-red color arises which is apparent with even one milligram of inosite. (Scherer.) The real sugars do not give this reaction.

4. If inosite is heated with a solution of cupric tartrate in potassic hydrate no reduction takes place, as in the case of

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\* Canstatt's Jahresber. 1859, II. Abth., p. 91 u. 98.

† Chem. Centralbl. 1869, p. 280.

‡ Annal. d. Chem., Band 160, p. 833.

grape sugar, but a green solution results, from which, after a time, a light greenish precipitate falls, while the fluid above becomes blue again. If this is filtered off, and the filtrate boiled again, the same change of color is observed. (Cloëtta.)

5. Neutral acetate of lead does not precipitate a solution of inosite, but on the addition of subacetate of lead, on the contrary, especially on heating, a transparent gelatinous precipitate occurs, which becomes white in a few moments, and exactly resembles paste. (Excellent means of separating inosite from animal and vegetable fluids.)

6. If a fluid containing inosite is evaporated to a few drops in a porcelain dish, and a small drop of a solution of mercuric nitrate is then added, a yellow precipitate is soon formed. If this is spread out as much as possible on the edge of the dish, and again warmed with great care, there remains, as soon as the fluid is all evaporated, if too much of the reagent has not been added, first a whitish-yellow residue, which soon becomes more or less dark red, according to the amount of inosite present. The color disappears on cooling, but reappears again on gently heating. Uric acid, urea, starch, sugar of milk, mannite, glycoll, taurin, cystin, and glycogen do not give this reaction. Albumen is colored red, and sugar is colored black, therefore neither of these substances should be present. (Gallois.)\* I have frequently made use of this reaction with the best result.

To prepare the mercuric solution, one part of mercury is dissolved in two parts of ordinary nitric acid, it is evaporated to one-half and treated with one and a half parts of water. After twenty-four hours the clear fluid is poured off from the basic salt.

D. *Detection.* As mentioned above, inosite was found in the urine of Bright's disease as well as in that of diabetes. The urine to be tested for inosite, after any albumen present is first separated, is completely precipitated with sugar of lead solution, filtered, and the warmed filtrate treated with subacetate of lead as long as any precipitate occurs. It is well to concentrate the urine to one-quarter of its bulk on the water bath before precipitation. The subacetate of lead precipitate, which contains the inosite combined with lead oxide, is collected after

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\* *Zeitschrift f. analyt. Chem.*, Band 4, p. 264.

twelve hours, and, after washing, is suspended in water and decomposed with sulphuretted hydrogen. After standing awhile a little uric acid first separates from the filtrate; the fluid is filtered from it, then concentrated as much as possible, and while boiling treated with three or four times its volume of alcohol. If a heavy precipitate results which adheres to the bottom of the glass, the hot alcoholic solution is simply poured off, but if a flocculent non-adhesive precipitate occurs, the hot solution is filtered through a heated funnel and allowed to cool. If after twenty-four hours groups of inosite crystals have deposited, they are filtered and washed with a little cold alcohol. In this case it is advisable to dissolve the precipitate obtained by the addition of the hot alcohol once more in as little boiling water as possible, and precipitate it a second time with three or four times its volume of alcohol, etc., in order to avoid any loss of inosite. If, however, no crystals of inosite have separated, ether is gradually added to the clear cold alcoholic filtrate, until a milky cloudiness results on shaking thoroughly, and it is then allowed to stand in the cold twenty-four hours. If too small an amount of ether has not been taken (an excess does no harm), almost all of the inosite present is separated in shining pearly leaflets. (Cooper, Lane.)\*

Inosite, however, appears to occur only very rarely in urine. Gallois investigated the urine of one hundred and two patients, but found inosite only seven times; it was found five times in thirty cases of diabetes together with sugar in very variable amounts, and twice in twenty-five cases of albuminuria.

## § 28. BILIARY SUBSTANCES.

Of the constituents of the bile, the biliary coloring matters as well as the biliary acids occur pathologically in the urine, especially in icterus, phosphorus poisoning, etc. The biliary acids have also been found at times in the urine in pneumonia without the biliary pigments having been discovered at the same time. In fatty degeneration of the kidneys cholesterin appears also to have been found in the urine.

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\*Annal. d. Chem. u. Pharm., Band 117, p. 118.

## BILIARY COLORING MATTERS.\*

A. *Presence.* The biliary coloring matters occur in the bile and biliary calculi in different modifications; we meet with them also in the contents of the intestine and in the excrement. Pathologically, especially in the severer forms of icterus, they appear in all of the fluids of the body and may even pass over into the tissues.

B. *Preparation.* Powdered gall-stones are freed from cholesterin and fat by treating them with ether; the residue is then boiled with water and treated with dilute hydrochloric acid. After washing and drying, the dark brownish green mass is boiled with chloroform as long as it continues to take up any pigment. After the chloroform is distilled off, the residue which remains is treated with absolute alcohol, by which a brown pigment, bilifuscin, is removed, while the red pigment (bilirubin — cholepyrrhin) remains behind. To purify the bilirubin it is repeatedly washed with ether and alcohol, then dissolved in chloroform, the solution allowed to evaporate until the pigment begins to separate, when it is precipitated by the addition of alcohol. A green coloring matter, biliprasin, is then withdrawn by alcohol from the residue of the gall-stones which has been left by the chloroform; this, after evaporation of the alcohol, remains behind, and may be purified by washing with ether and chloroform, and dissolving again in a very little cold alcohol. Finally, after this treatment of the gall-stones there remains a brown body, bilihumin, insoluble in water, alcohol, ether, chloroform and dilute acids.

C. *Chemical Properties.*

a. *Bilirubin (Cholepyrrhin)*,  $C_{42}H_{66}N_4O_6$  [ $C_{32}H_{48}N_4O_6$ ]. Bilirubin, besides in the bile, is found in the urine in icterus, etc. It is without doubt identical with the hæmatoidin crystals occurring in old extravasations of blood. (Hoppe-Seyler.)† If faintly acidified bile is directly shaken with chloroform, bilirubin remains behind after the evaporation of the chloroform in microscopic red tables and prisms, belonging to the rhombic

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\* Annal. d. Chem. und Pharm., Band 132, p. 823. Journal f. pr. Chem., Band 104, p. 28, 193, and 401.

† Handbuch d. physiol. Analyse, 3<sup>o</sup> Aufl., p. 203.



system. It is obtained from gall-stones according to the above method, as an amorphous orange-colored powder. Bilirubin is insoluble in water, very difficultly soluble in ether and alcohol, but readily soluble in hot chloroform, benzole, and bisulphide of carbon. The solutions even on considerable dilution still have a yellow color.

1. An ammoniacal solution of bilirubin gives with chloride of calcium, chloride of barium, acetate and subacetate of lead, and nitrate of silver precipitates which are insoluble in chloroform.

2. An alkaline solution of bilirubin, treated with an equal volume of alcohol and then with a little concentrated commercial nitric acid, gives rise to a magnificent play of colors. The yellow color first changes to a green, then blue, violet, ruby red, and at last dirty yellow. If shaking is avoided in the performance of this test, all of these colors appear in layers, one above the other. The play of colors also appears without the addition of alcohol, but then a few drops of red fuming acid must be added to the nitric acid. The limit of the reaction first begins at a dilution of from seventy to eighty thousand.

This reaction is very elegant and positive if a dilute solution of bromine in alcohol or simple bromine water is added drop by drop to a solution of bilirubin in chloroform. (Maly.)

Maly has prepared the final yellow end-product of this reaction, and named it choletelin. Choletelin, however, is not identical with urobilin or hydrobilirubin, as has been affirmed by some. (Maly.)\*

Characteristic changes of the spectrum correspond to this color-reaction. If the color of the solution approaches the blue modification, a dark absorption band appears between the lines C and D, beginning somewhat nearer D and reaching to about midway between D and E. On dilution the band resolves into two rather indistinct bands,  $\alpha$  and  $\beta$ , which are separated by a narrow clear space situated nearer to D. In the further progress of the reaction these lines gradually diminish in intensity, but remain apparent up to the beginning of the red modification. Almost at the same time with  $\alpha$  and  $\beta$ , but usually a little later, a third band,  $\gamma$ , appears between b and F almost

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\* *Zeitschrift f. analyt. Chemie*, Band 11, p. 858; *ibid.*, Band 12, p. 836.



exactly bounded by this last line, increasing in distinctness in proportion as the former bands become paler, and attaining its greatest intensity toward the end of the reaction, but finally it also disappears as the action of the nitric acid progresses. It is interesting that this band,  $\gamma$ , corresponds to the absorption band,  $\gamma$ , of urobilin. (See Urobilin.) (Jaffé\* and Fudakowski.)†

3. A solution of bilirubin in an excess of sodic hydrate becomes green when exposed to the air. Bilirubin, by taking up oxygen, becomes converted into biliverdin. (Maly.)‡

b. *Biliverdin*,  $C_{16}H_{18}N_2O_4$  [ $C_{32}H_{18}N_2O_8$ ]. Biliverdin occurs probably in icteric urine, which has become green after long standing. It dissolves in alcohol with a beautiful green color; in water, ether, and chloroform it is insoluble.

1. In alkalies biliverdin dissolves with a green color in contradistinction to biliprasin, which produces with alkalies a brown. On long standing of the alkaline solution biliverdin finally becomes converted into biliprasin.

2. An alkaline solution of biliverdin reacts with nitric acid the same as bilirubin. The color first becomes blue, then violet, red, and lastly dirty yellow.

Bilirubin and also biliverdin can be changed to urobilin (hydrobilirubin) on treatment with sodium amalgam. (Maly.)

c. *Biliprasin*,  $C_{16}H_{22}N_2O_6$  [ $C_{32}H_{22}N_2O_{12}$ ]. Biliprasin occurs in small quantity in gall-stones. It also probably occurs in the bile of the ox and in icteric urine.

1. Biliprasin is insoluble in water, ether, and chloroform. Alcohol dissolves it with a beautiful green color, which becomes brown on the addition of ammonia. (Distinction from biliverdin.)

2. Biliprasin readily dissolves in alkalies. Dilute solutions have the same color as strongly pigmented icteric urine. (On the addition of an acid the brown color becomes green again. Distinction from bilifuscin.) When brown icteric urine on spontaneous acidification, as well as after the addition of an acid, shows the same change of color, it must be concluded that biliprasin is present in preponderant amount. (Städeler.)

\* Journ. f. pr. Chem., Band 104, p. 401.

† Zeitschrift f. analyt. Chem., Band 8, p. 516.

‡ Journ. f. pr. Chem., Band 104, p. 84.

3. An alcoholic solution of biliprasin shows the same reaction with nitric acid as bilirubin and biliverdin, only the blue is very faint and indistinct.

d. *Bilifuscin*,  $C_{16}H_{20}N_2O_4$  [ $C_{32}H_{40}N_4O_8$ ]. This brown pigment has been thus far found only in small amount in human gallstones. It dissolves in alcohol and potassic hydrate with a brown color; it is precipitated from alkaline solutions in brown flocculi by hydrochloric acid. Bilifuscin behaves the same with nitric acid as the other pigments.

D. *Detection*. A urine which contains biliary pigments in large amount is always strongly tinged deep brown, reddish brown, greenish brown, dark green, or grass green. It foams strongly on being shaken, and colors a piece of filter paper dipped into it yellow or greenish.

1. The reaction for the biliary coloring matters, even when present in very small amount, is most easily obtained by pouring into a conical test glass about an inch of concentrated nitric acid, which has been somewhat decomposed by standing in the light, and then carefully covering it with a layer of the urine to be examined by means of a pipette. If biliary pigment is present, the play of colors begins at the point of contact of the two fluids with a beautiful green ring which gradually rises, and on its lower border a blue, violet, red, and finally yellow ring gradually appears. (Kühne.) It is to be observed here, however, that all of these colors do not always occur; violet and green, for the most part, are the most permanent, and the green which first occurs, is alone demonstrative of biliary pigment, since red and violet rings also occur with uroxanthin (indican) and its products of decomposition. (See Uroxanthin.) The presence of albumen by no means disturbs the reaction, since the albumen coagulated by nitric acid, usually carries down at the same time a portion of the pigment, and thus shows the reaction in the most beautiful manner. But at all events the nitric acid ought not to contain too much nitrous acid, since in this case the reaction runs a very rapid course, and the colors are rapidly destroyed.

In order to avoid a possible confusion between bilirubin and indican, Vitali\* performed the test for the biliary pigments

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\* Jahresbericht u. d. Fortschritte der Thierchemie, 1873, p. 149.

with nitrate of potassium and dilute sulphuric acid. A single drop of a solution of nitrate of potassium and a few drops of sulphuric acid suffice to produce a beautiful green color in a urine containing only mere traces of bile. After a time the color disappears and becomes yellow at once, without having previously passed through red and blue.

2. The slightest traces of bilirubin can finally be detected in urine, even when the above reaction fails, if large amounts of urine are successively shaken with chloroform, the urine extracted being frequently poured off. The smallest amounts of bilirubin are taken up by the chloroform, and sink with it to the bottom, giving it a yellow color. The supernatant urine is then removed and the chloroform solution covered with a layer of nitric acid which contains nitrous acid. The reaction now takes place from above downward, and shows very brilliantly even with the smallest traces of bilirubin. Another part of the chloroform solution is allowed to evaporate in the air, and the residue is examined microscopically. If bilirubin is present, single reddish-yellow crystals will be readily discovered, which show the color reaction with nitric acid very beautifully under the microscope. The crystals readily dissolve in alkalis; the solution becomes green on standing exposed to the air.

If in this reaction the chloroform should not readily and quickly settle, the urine is evaporated to dryness on the water bath, the residue is extracted with water, filtered, washed, dried, and the filter cut into small pieces, and repeatedly extracted with chloroform while warm. The golden-yellow solution which is obtained is directly tested for bilirubin with nitric acid or bromine water. Frequently traces of bilifuscin can still be obtained by boiling alcohol from the residue, which has been exhausted with chloroform. (Schwanda.)\*

It is not advisable to test an alcoholic solution for biliary pigments with nitric acid, since alcohol also, in the absence of biliary pigments, readily gives a similar play of colors, owing to the formation of hyponitric acid. Finally, if a urine together with biliary coloring matter contains hæmoglobin also, the former is precipitated with subacetate of lead, the washed precipitate is decomposed with carbonate of sodium, and the filtrate used for testing with nitric acid.

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\* *Zeitschrift f. analyt. Chem.*, Band 6, p. 501.

3. Cases not rarely occur, however, where the specified reactions for biliary coloring matters remain absent, even when quite large quantities of pigment are present. According to the investigations of Prussak,\* continued fever has an influence on the failure of the reaction; and Huppert† believes that he has found that in such cases the urine contains no bilirubin but only biliprasin. To detect the latter, according to Huppert, the following method is used: The urine is precipitated with milk of lime; the precipitate is collected, and while still moist is put into a reagent glass, which is then half filled with absolute alcohol, and dilute sulphuric acid is added until the fluid, after shaking, has a distinct acid reaction. It is heated, the precipitate filtered off, and the filtrate heated to boiling. The greenish-yellow or yellowish-green color of the fluid then changes quickly to a beautiful dark green, if an excess of sulphuric acid is present, this change taking place the sooner the more free acid there is. Under certain circumstances not thoroughly investigated, however, the fluid at times, on continued boiling, becomes dark blue.

But this method is not sufficient in all cases, since, according to Fudakowski,‡ products of the oxidation of bilirubin, which form compounds with lime only with difficulty, occur not infrequently in icteric urines. In that case it is more accurate to precipitate with subacetate of lead or sugar of lead and ammonia, and decompose the washed precipitate with oxalic or sulphuric acid. The aqueous oxalic acid solution is evaporated to dryness, the pigment is extracted from the residue with chloroform, and the acid solution thus obtained is tested with the spectroscope. The absorption band,  $\gamma$ , between b and F, described above under Bilirubin, will be perceived more or less dark and sharply defined, according to the concentration. Frequently this absorption band can be detected if the urine, after sufficient dilution, is examined directly with the spectroscope in a layer two cm. thick.

Investigations by A. Heinsius and F. Campbell§ have proved that the icteric urine in these cases contained only cholete-

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\* Centralbl. f. d. med. Wissenschaft., 1867, p. 97.

† Zeitschrift f. analyt. Chem., Band 6, p. 291 u. 498.

‡ Zeitschrift f. analyt. Chem., Band 8, p. 516.

§ Archiv der Physiologie, Band 4, p. 497.

lin, the final yellow product of oxidation, which is formed in Gmelin's test, and consequently cannot give the well-known change of colors on the addition of nitric acid. The familiar spectral appearance which characterizes the end of Gmelin's reaction can be readily obtained, however, with such urine, especially after acidifying with hydrochloric acid.

### § 29. BILIARY ACIDS.

The basis of all of the acids occurring in bile is the non-nitrogenous cholic acid,  $C_{24}H_{40}O_6$ ,  $[C_{23}H_{38}O_6 + HO]$ . When pure it crystallizes in colorless shining tetrahedra, rarely in quadrilateral octahedra. It is not contained in the bile as such, but is united with taurin as taurocholic acid and with glycocoll as glycocholic acid.

If cholic acid is heated to  $190^\circ$  or  $200^\circ$  C., or boiled for a long time with acids, it decomposes into dyslysin,  $C_{11}H_{18}O_3$ ,  $[C_{10}H_{16}O_3]$ , and water. Dyslysin is insoluble in water and alcohol; very slightly soluble in ether. On being boiled with an alcoholic solution of hydrate of potassium it becomes cholic acid again. The barium salt of cholic acid dissolves with much difficulty in cold water, more easily in hot water, and very readily in alcohol.

1. *Taurocholic acid*,  $C_{25}H_{41}NSO_6$ ,  $[C_{24}H_{39}NSO_6]$ . This acid, occurring in the bile in combination with sodium, has not yet been obtained in a crystalline form. When not absolutely pure it forms a white, amorphous, very hygroscopic powder having an intensely bitter taste, readily soluble in alcohol and water, and insoluble in ether. The barium salt of taurocholic acid is readily soluble in water. If taurocholic acid is treated a long time with potassic hydrate at a boiling temperature, it decomposes into cholic acid, which combines with potassium, while taurin is set free; if hydrochloric acid is used instead of hydrate of potassium, it splits up in the same manner; the cholic acid, however, is not separated as such, but is changed partially into dyslysin by the action of the hot hydrochloric acid.

The separated taurin,  $C_2H_5SNO_2$ ,  $[C_2H_5S_2NO_2]$ , crystallizes in colorless, regular, six-sided prisms with four- and six-sided terminations. (Funke, Taf. III., fig. 4; 2<sup>e</sup> Aufl., Taf. V., fig. 1.) This body contains nitrogen, and is characterized by containing

twenty-five per cent. of sulphur. Taurin is readily soluble in water, less readily in alcohol; the solutions have a perfectly indifferent behavior toward vegetable colors.

Taurin is most readily obtained by evaporating fresh ox-bile free from mucus with strong hydrochloric acid, when the dyslysin, etc., separates. The chloride of sodium is allowed to crystallize from the strongly concentrated fluid, the mother liquor is evaporated somewhat further, and the taurin is precipitated by admixture with double its volume of strong alcohol. It is obtained pure in the form of beautiful large crystals by recrystallization from water.

2. *Glycocholic acid*,  $C_{26}H_{43}NO_8$ ,  $[C_{25}H_{41}NO_{11} + H_2O]$ . This occurs also in normal bile in combination with sodium. Glycocholic acid crystallizes in the form of very fine needles (Funke, Taf. IV., fig. 6; 2<sup>o</sup> Aufl., Taf. VIII., fig. 5), wherein it essentially differs from taurocholic acid. It is quite readily soluble in hot water and alcohol, but on the contrary is very slightly soluble in ether. It does not crystallize from the alcoholic solution, but separates as a resinous mass on evaporation; if, however, the solution is mixed with water, it gradually separates in the crystalline form on evaporation. The barium salt of glycocholic acid is readily soluble in water. By boiling with potassic hydrate, baryta water, or hydrochloric acid, it suffers a similar decomposition as taurocholic acid, cholic acid or dyslysin being set free and glycocoll separated.

Glycocoll,  $C_4H_7NO_3$ ,  $[C_4H_7NO_3]$ , is formed by treating gluten with mineral acids, from monochloroacetic acid by the action of ammonia, and finally from hippuric and uric acids by heating with hydrochloric acid; from uric acid at a temperature of 160° to 170° C. Glycocoll forms colorless rhombic prisms (Funke, Taf. III., fig. 5; 2<sup>o</sup> Aufl., Taf. IV., fig. 1), which are hard and permanent in the air, and taste almost as sweet as cane sugar. This body contains nitrogen but no sulphur.

A. Emmerling\* has discovered a new method for the synthesis of glycocoll. If cyanogen gas is treated with concentrated hydriodic acid, glycocoll is formed according to the following reaction:




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\* Ber. d. d. chem. Gesellsch., Band 6, p. 1851.

*Chemical Properties.*—1. All of the biliary acids when combined, as well as free cholic acid also, react in a peculiar characteristic manner with sulphuric acid and sugar, which distinguishes them from the coloring matters, as well as from taurin and glycocoll. If the aqueous solution of any one of the biliary acids is treated with a few drops of a solution of sugar and then with concentrated sulphuric acid until the mixture has a temperature of 50° to 70° C., the fluid becomes colored a beautiful purple violet. (Pettenkofer.) Oleic acid and albumen give a similar reaction.

To distinguish this from similar reactions which are obtained with albuminous bodies, oleic acid and amyl alcohol, the spectral appearances of the biliary acid reaction can be used. If the fluid is diluted, so that only the violet is absorbed, an absorption band on the line F and a second between D and E, nearer E, appear. In concentrated solutions only the second band can be seen. (L. Schenk.)\*

Even the smallest traces of biliary acids can be detected by means of this reaction in the following manner: A few drops of the fluid to be tested are evaporated to dryness on the water bath in a porcelain dish; a small drop of a solution of sugar (one gram of sugar in half a liter of water) and an equally small drop of concentrated sulphuric acid are added to it. It is then heated a few minutes on the water bath, and the violet-red color soon forms on the edge. At this moment the dish is removed from the water bath and allowed to stand quietly, when the reaction will increase considerably in intensity. In this manner I have succeeded in detecting with absolute certainty, by the most beautiful reaction, one four-hundredth to one six-hundredth of a milligram of the sodium salt of the biliary acids. On heating on the water bath, the reaction occurs much more positively than by evaporating over a free flame, as recommended by Neukomm.

2. A second very delicate reaction is the following: The biliary acid or salt is covered with a small amount of concentrated sulphuric acid, moderately warmed, and then water is added. The resinous flakes which deposit are separated from the acid, washed a few times with water without completely removing the sulphuric acid, and gently heated in a porcelain

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\* Jahresbericht u. d. Fortschritte d. Thierchemie, Band 2, p. 232.



dish until they become colored. Then the residue is taken up with a very little alcohol, and the green solution is evaporated with constant turning, so that the inner surface of the dish becomes covered with a deep indigo-colored coating, even when only a very little acid has been used. If the biliary acids are mixed with foreign matters, or if the sulphuric acid is allowed to act a long time, or at too high a temperature, the coating of pigment appears green.

According to my experience, however, this reaction, even with the modification proposed by Von Bogomoloff,\* is far less delicate and accurate than Pettenkofer's.

*Detection.*—1. A portion of urine (300 to 500 cc.) is evaporated on the water bath almost to dryness, and the residue is extracted with ordinary alcohol; the alcoholic solution is evaporated again, and the residue extracted with absolute alcohol. The solution thus obtained, now tolerably poor in salts, is freed from alcohol, the residue is taken up with a little water, the solution treated with subacetate of lead, of which an excess is to be carefully avoided, and the precipitate, after standing about twelve hours, is collected, washed, and gently dried between blotting paper. In order to remove as much as possible of other substances mixed with the lead precipitate, the lead compound with the biliary acid is extracted with boiling alcohol, the solution is evaporated to dryness after the addition of carbonate of sodium, and the residue is treated with absolute alcohol in order to obtain the sodium compound with the biliary acid. The sodium salt thus obtained always contains, in addition to the biliary acids, small amounts of a resinous constituent of the urine, which is colored brownish red by sulphuric acid, at times also pale blue or violet, and on heating, after the addition of sugar, reddish or yellowish brown. This color is seldom so deep as to conceal the biliary reaction; but if this is found to be the case, after a preliminary trial, the biliary acid is once more precipitated from the aqueous solution by subacetate of lead, the precipitate is collected after standing awhile and decomposed, as above, with carbonate of sodium. Then two or three drops of a solution of sugar (one part of sugar to four parts of water) are added to the aqueous solution of the

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\* *Zeitschr. f. analyt. Chem.*, Band 9, p. 148.



sodium compound made as concentrated as possible, and afterward pure concentrated sulphuric acid, free from nitric and sulphurous acid, is added. Care is to be taken here that the temperature does not rise much above 70° C. If biliary acids are present the fluid first becomes cloudy, then clear, and at the same time yellow, but shortly afterward it changes to a pale cherry-red, dark carmine-red, and at last beautiful purple violet.

The test becomes considerably more delicate, if it is performed with the modification given above; one four-hundredth of a milligram of the sodium salt of the biliary acid can be detected with absolute certainty by this procedure. The presence of biliary acids can be considered as proved only when the fluid becomes colored not only red, but also distinctly purple violet.

The biliary acids may frequently be successfully detected by the following very simple method: A piece of filter paper is dipped into the urine to be tested after a little cane sugar has been previously added, and then the paper is allowed to dry. If a drop of pure concentrated sulphuric acid is then placed on the paper by means of a glass rod, there appears in about a quarter of a minute a beautiful violet color which is quite distinct, especially with transmitted light. This method is, in fact, very delicate, so that three one-hundred-thousandths (0.00003) of a gram of biliary acid gives the reaction in a most beautiful manner. Normal urine does not give this reaction. If a large amount of cane sugar is present, a reddish or brown color, which, however, cannot be confounded with Pettenkofer's reaction, appears. (G. Strassburg.)\*

2. According to Hoppe the urine is directly precipitated with subacetate of lead and a little ammonia, the precipitate washed with a little water, and then boiled with alcohol and filtered while hot. The alcoholic filtrate is treated with a few drops of sodic hydrate solution, evaporated to dryness, and the sodium salt of the biliary acids extracted from the residue by boiling with absolute alcohol. The alcoholic solution is evaporated to a small volume, and treated in a closed flask with ether, by which the biliary salts are precipitated and often

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\* Archiv der Physiologie, Band 4, p. 461.

crystallize out after long standing. In the employment of the test with sugar and sulphuric acid it is not necessary to wait, however, until the precipitate caused by ether has become crystalline, but the resinous precipitate dissolved in a little water can be immediately used for this purpose. If, however, we wish to determine whether cholic acid is present in addition to glycocholic and taurocholic acids, the resinous precipitate is allowed to crystallize under ether, the ether is then poured off, the crystals dissolved in a little water and treated with a drop of chloride of barium solution. If a precipitate takes place, the presence of cholic acid, whose barium salt is very difficultly soluble in water, is demonstrated. (Hoppe-Seyler.)

3. According to Dragendorff, the biliary acids can be withdrawn from the urine by shaking with chloroform. 120 to 150 grams of urine are acidulated with a few drops of hydrochloric acid, and shaken with 30 grams of chloroform for at least an hour. The urine is separated by decanting, and the chloroform, which is colored brown by the precipitation of the extractive and coloring matters, is treated with six to eight cc. of absolute alcohol, which takes up the cloudy flakes while the chloroform becomes perfectly clear again. It is then filtered, when a thick jelly frequently forms on the filter which contains the chloroform, and allows nothing more to flow through. If this jelly is detached from the filter, however, by stirring with a glass rod, the chloroform and alcohol pass through rapidly. The chloroform separated from the alcohol is then allowed to evaporate on watch glasses, and the residue is used for the test with sugar and sulphuric acid. By this method Vogel\* found biliary acids in the urine of eight different healthy persons. To decide the question whether biliary acids really belong to the normal constituents of urine, Dragendorff then examined 1,000 cc. of the urine of each of ten healthy persons, varying in age from eight to fifty-five years, by the method given above under Detection. The sodium salt of the biliary acid which remained after the evaporation of the alcoholic solution was dissolved in acidulated water, and the free biliary acid transferred to chloroform by shaking with it. The residue which remains after evaporation of the chloroform serves for

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\* Zeitschrift f. analyt. Chem., Band 11, p. 467.

Pettenkofer's test. By working with one hundred liters of normal urine, according to the method given, Dragendorff succeeded in preparing the biliary acids in pure form; a part separated as the sodium salt of the biliary acids in microscopic crystals, and the elementary analysis gave corresponding results. Dragendorff obtained from one hundred liters of normal urine 0·7 to 0·8 gram of biliary acids.

It is always advisable to take large quantities of urine for working, since always only very small amounts of the biliary acids go over into the urine, even when the icterus is very intense.

Cholesterin has sometimes been found in the urine in fatty degeneration of the kidneys, mixed with other fats. The sediment, consisting chiefly of fat globules, was collected, dried on a water bath, and digested with a mixture of alcohol and ether. The filtered and concentrated extract deposited crystallized cholesterin, which, on account of its microscopic form, is not readily confounded with any other substance. (Funke, Taf. VI., fig. 1.)

If a little cholesterin is dissolved in about two cc. of chloroform, and then about an equal volume of concentrated sulphuric acid is added and the fluid shaken, the chloroform solution becomes rapidly colored blood red, and then beautiful cherry red or purple, a color which remains unchanged for days. The sulphuric acid, standing under the chloroform at the same time, has a strong green fluorescence. If some of the chloroform solution is poured into a saucer, it rapidly becomes blue, then green, and finally yellow, due to the absorption of water. (Salkowski.) The reaction is elegant and delicate.

### § 30. LACTIC ACID.

Formula : $C_3H_5O_3$ [ $C_3H_5O_3$ ]	{	Carbon	40·00
		Hydrogen	6·67
		Oxygen	53·33
			100·00

A. *Presence.* Ordinary lactic acid from fermentation occurs partly free, partly in combination, in the juices of the stomach and contents of the intestine, and in fermenting diabetic urine

as well as in sour milk. Paralactic acid occurs in the muscular juice of man and animals, in the bile, as well as very abundantly in the urine after phosphorus poisoning.\* It has also been found in the urine in acute atrophy of the liver,† trichinosis,‡ and osteomalacia.§ Whether the lactic acid contained in different glandular fluids and transudations is ordinary or paralactic acid, requires still more accurate investigations.

Lehmann has found that when the excretion of oxalate of calcium and uric acid is increased, lactic acid is always found in the urine.

Hoppe-Seyler obtained lactic acid, together with brenzcatechin, by the action of alkalies on sugar.

According to the investigations of Wislicenus,|| the lactic acid of flesh is a mixture of two different acids, the principal one of which turns the plane of polarized light toward the right, and forms well-crystallizable salts, while the second acid occurs in less amount and possesses only a slight power of crystallization. Wislicenus found this second acid in ordinary meat in greater amount than in Liebig's meat extract, and in still greater relative amount in various pathological fluids of the animal and human body, such as urine, ascitic fluid, bile, etc. The optically active lactic acid of meat yields on oxidation with chromic acid no malonic acid; it is not, therefore, ethylenlactic acid, with which the second is probably identical, which does yield malonic acid together with carbonic and oxalic acids on being oxidized with chromic acid.

*B. Chemical Properties.* In the pure concentrated condition lactic acid is a colorless and odorless syrupy fluid, which hitherto has never been crystallized, and has a strongly acid taste. It is soluble in water, alcohol, and ether, and attracts water from the air. At 140° it becomes free from water; but at a higher temperature it splits up into lactid, carbonic acid, and other compounds.

There are no characteristic tests for lactic acid, but the

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\* O. Schultzen u. L. Riess: Ueber acute Phosphorvergiftung und acute Leberatrophy.

† Ibid.

‡ Berichte d. deutsch. chem. Gesellsch., 1871, Heft 3.

§ Moers u. Muck: Deutsches Archiv f. klin. Med., Band 5, p. 485.

| Annal. d. Chem. und Pharm. 167, p. 346. Tagblatt der 46 Versammlung deutsch. Naturforscher u. Aerzte, Wiesbaden.

microscopic appearance of some of its salts is distinctive and very important for its recognition.

1. *Lactate of Calcium.* This is formed by dissolving carbonate of calcium in lactic acid. It crystallizes under the microscope in fine needles collected in tufts. Of these tufts two are always so placed with their pedicles toward each other that they resemble pencils which run into each other. (Funke, Taf. II., fig. 1; 2<sup>te</sup> Aufl., Taf. I., fig. 4.)

Ordinary lactate of calcium contains 29.22 per cent. of water of crystallization, while paralactate of calcium contains 24.83 per cent.

2. *Lactate of Zinc.* This is formed by boiling pure oxide of zinc with lactic acid. The crystals, when separated rapidly under the microscope, appear in the form of spherical groups of needles, and may be readily obtained in great beauty. If, however, we allow a drop of a solution of lactate of zinc to evaporate gradually, the crystals first appear club-shaped, truncated at both ends. These crystals gradually increase, the ends become smaller, while the middle becomes bellied. This peculiar bellied, barreled, or clubbed shape is very distinctive and characteristic of lactate of zinc. (Funke, Taf. II.; 2<sup>te</sup> Aufl., Taf. I., fig. 5.)

Ordinary lactate of zinc contains 18.18 per cent. of water of crystallization; paralactate, however, contains 12.90 per cent.

C. *Detection.* The urine, which must be fresh, is evaporated almost to dryness on the water bath, and the residue treated with an alcoholic solution of oxalic acid. The oxalates which are thus formed, as well as the oxalate of urea, remain undissolved, while the lactic acid, together with the phosphoric and hydrochloric acids, are in solution. The fluid is digested with hydrate of lead, evaporated to dryness, and the residue extracted with absolute alcohol which will dissolve the lactate of lead. The filtrate is treated with sulphuretted hydrogen, after filtering evaporated on the water bath to a syrup, and shaken with ether, which, after evaporation, leaves the lactic acid more or less pure. This is dissolved in a little water, boiled with zinc-oxide, filtered, and allowed to crystallize gradually on an object glass. The lactate of zinc is readily recognized by its barrel and club-shaped crystals, especially those which increase in size.

Scherer uses the following method for detecting lactic acid, which yields excellent results in every way: The extract which is to be tested for lactic acid is dissolved in water, precipitated with baryta water, and filtered. Any volatile acids present are removed from the filtrate by distillation with a little sulphuric acid, and the residue is allowed to stand several days with strong alcohol. The acid fluid is evaporated with a little milk of lime to dryness, the residue is dissolved in hot water, and while still warm is filtered from the excess of lime and sulphate of calcium, a stream of carbonic anhydride is conducted into the filtrate, it is heated again to boiling, filtered from the precipitated carbonate of calcium, the fluid evaporated to dryness, the residue warmed with strong alcohol, filtered if necessary, and the neutral filtrate set aside for a few days for the lactate of calcium to separate. If so little lactic acid is present that no crystals separate, it is evaporated to a syrup, mixed with strong alcohol and allowed to stand, when a usually dark deposit of extractive matter and lime is formed. The fluid is then poured into a closed vessel, and a small amount of ether is gradually added. Even traces of lactate of calcium, which can be readily recognized under the microscope, separate.

Large amounts of lactic acid, such as occur in the urine after phosphorus poisoning, are separated in the following manner: The urine is strongly concentrated on the water bath, and then completely precipitated while warm with 95 per cent. alcohol. After twenty-four hours the clear alcoholic solution is decanted from the sediment, evaporated to a syrup, acidified with dilute sulphuric acid, and shaken with renewed quantities of ether as long as it takes up anything. After distilling off the ether the residue is dissolved in water, filtered, precipitated with sugar of lead solution, filtered, the filtrate treated with sulphuretted hydrogen, filtered again, and the acetic acid expelled by repeated evaporation on the water bath. The colorless fluid thus obtained is saturated with carbonate of barium, filtered, evaporated to a syrup, and the lactate of barium precipitated with absolute alcohol. The mass, which is at first doughy, is changed into a granular crystalline powder by continued digestion with absolute alcohol, and its aqueous solution is accurately precipitated with sulphate of zinc, so as to form lactate of zinc. The zinc salt after evaporation separates from the filtrate in crystals.

with 12.9 per cent. of water of crystallization, and 26.74 per cent. of zinc.\*

### § 31. VOLATILE FATTY ACIDS.

Of the volatile fatty acids there have thus far been found in the urine formic, acetic, propionic, butyric, and valerianic acids.

I. *Formic Acid*,  $\text{CH}_3\text{O}$ ,  $[\text{C}_2\text{H}_3\text{O}_2]$ . Formic acid, besides in ants, occurs also in the poison-organs and stings of certain insects. It was, moreover, found in the sweat, in the fluid of the spleen, pancreas, thymus gland, muscles, and brain. Finally it occurs in the blood as well as in the urine, according to Buliginsky† and Thudichum.‡ It is formed by the decomposition of the coloring matter of the blood by acids; also, according to Thudichum, by the decomposition of urochrom. Somewhat larger amounts of formic acid appear to occur in the urine of leukæmia. (E. Salkowski.)

*Chemical Properties.* Pure formic acid is a colorless fluid of intense piercing odor, which freezes at  $0^\circ$ , boils at  $100^\circ \text{C}$ ., and mixes with water and alcohol in every proportion.

1. Ferric chloride causes a blood-red color in neutral solutions of formiates.

2. Nitrate of silver does not precipitate free formic acid; it precipitates formiates only when in concentrated solutions. Formiate of silver becomes black in the cold; on heating complete reduction immediately takes place. This reduction, in which the fluid is colored black, takes place even when the solution is so dilute that no precipitate occurs, or when free formic acid is present.

3. If a solution of formic acid or one of an alkaline formiate is treated with mercuric chloride, and heated to  $60^\circ$  or  $70^\circ \text{C}$ ., mercurous chloride (calomel) separates, and after more prolonged boiling the metal also. Free hydrochloric acid prevents this reaction.

4. On heating with concentrated sulphuric acid formic acid decomposes into carbonic oxide and water.

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\* O. Schultzen and L. Riess, loc. cit.

† Hoppe-Seyler, Med. chem. Mittheilungen, Heft 2, p. 240.

‡ The Journ. of the Chemical Society, vol. 8, p. 400.



II. *Acetic Acid*,  $C_2H_4O_2$ ,  $[C_2H_3O_2]$ . Acetic acid appears in the urine as soon as it has commenced to ferment. It also occurs in quite an amount during the fermentation of diabetic urine. It has been found also in muscular juice and in the fluid of the spleen, in leukæmic blood, in the contents of the stomach and vomitus together with free lactic acid in cases of disturbed digestion, in the sweat, and in the bile. According to Thudichum, acetic acid is also a product of the decomposition of urochrom.

*Chemical Properties.* In the concentrated state acetic acid is a colorless fluid with an intensely acid smell and a sharp caustic taste, whose boiling point is  $119^\circ C$ . At  $5^\circ C$ . it crystallizes; above  $16^\circ C$ ., however, it is fluid. Acetate of sodium crystallizes readily.

1. Ferric chloride gives in solutions of an acetate a blood-red color of acetate of iron.

2. Nitrate of silver gives in neutral solutions of an acetate a white crystalline precipitate of acetate of silver, which dissolves in hot water without reduction, and on cooling crystallizes out again.

3. On heating an acetate with alcohol and sulphuric acid the characteristic odor of acetic ether is evolved; with sulphuric acid alone the piercing odor of acetic acid is obtained.

Crystallized acetate of sodium contains 22.9 per cent. of sodium, the barium salt 53.8 per cent. of barium, the silver salt 64.67 per cent. of silver.

III. *Propionic Acid*,  $C_3H_6O_2$ ,  $[C_3H_5O_2]$ . Propionic acid is said to occur in the fluids of certain glands, in the sweat, in the gastric juice, in the vomitus in cholera, and in fermenting diabetic urine as well as in the bile. Salkowski\* mentions that he has found it also in normal urine.

*Chemical Properties.* The concentrated acid is a colorless oily fluid, which boils at  $138^\circ C$ ., has a peculiar odor and is readily soluble in water. The addition of a large amount of chloride of calcium separates it from its aqueous solution as an oily fluid.

1. Nitrate of silver gives in concentrated solutions of propionates a whitish precipitate, which is soluble with partial reduc-

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\* Archiv d. Physiolog., Band 2, p. 361.



tion in boiling water. When the solution cools the propionate of silver crystallizes in white, shining, microscopic rosettes of needles.

2. The propionate of barium is readily soluble in water, and crystallizes in octahedral prisms with oblique terminal surfaces.

Propionate of silver contains 59.67 per cent. of silver, and the barium salt 48.41 per cent. of barium.

IV. *Butyric Acid*,  $C_4H_8O_2$ ,  $[C_3H_7O_2]$ . Butyric acid occurs in the sweat, in the contents of the stomach and in the vomitus in disturbances of the digestion, in the contents of the large intestine, in the solid excrement, and in the urine. It has also been found in the blood, juice of the spleen, contents of ovarian cysts and in the muscular juice. Lehmann found it at times in the urine of pregnant women, but also in that of women not pregnant; he has also frequently found butyric acid in the urine of men.

If diabetic urine is treated with powdered chalk, and the mixture is allowed to ferment at a temperature of  $35^\circ$  to  $40^\circ$  C., a considerable amount of butyric acid forms (Scherer, written communication), while at a lower temperature, without the addition of chalk, it often contains only acetic acid.

*Chemical Properties.* The pure acid is an oily, colorless fluid, which smells very disagreeably like rancid butter, and which boils at  $157^\circ$  C. It is soluble in all proportions in water, alcohol, and ether. Chloride of calcium separates it from the concentrated aqueous solution as an oily layer of fluid.

Most of the salts of butyric acid are soluble in alcohol and water, and on the addition of mineral acids develop the disagreeable odor.

1. Butyric acid forms compounds with the alkalies, alkaline earths, and the true metallic oxides. The compounds with the alkalies are deliquescent and uncrystallizable, while the other salts can be readily obtained in a crystalline form.

a. *Butyrate of Barium.* This can be produced by saturating butyric acid with baryta water. If the compound is crystallized rapidly from such a solution it separates in the form of a pellicle shining like fat on the surface of the fluid, and appears under the microscope mostly in the form of close heaps of crystalline plates not accurately distinguishable. If, however, the solution of butyrate of barium is allowed to evaporate spontaneously, long,

flattened, completely transparent prisms form, which lie together for the most part in stellate rosettes. This salt dissolves readily in water; the solution blues reddened litmus paper. (Funke, Taf. I., fig. 8; 2<sup>te</sup> Aufl., Taf. II., fig. 2.) Butyrate of barium contains 44.05 per cent. of barium.

b. *Metallic Butyrates* are formed by precipitating a concentrated solution of the butyrate of an alkali with the solutions of the various metallic oxides. Thus the nitrate of silver produces a yellowish-white crystalline precipitate of butyrate of silver, which is almost insoluble in cold water and contains 55.38 per cent. of metallic silver.

V. *Baldrianic Acid*,  $C_8H_{10}O_4$ ,  $[C_{10}H_{10}O_4]$ . Baldrianic acid has been found in the urine in typhoid fever, variola, and acute atrophy of the liver. It is formed very abundantly by the putrefaction of impure leucin in contact with ammonia.

*Chemical Properties.* The pure acid is a colorless, oily fluid of penetrating odor, which boils at 175° C., and is readily soluble in alcohol and ether. It requires thirty parts of water, however, to dissolve it.

1. The baldrianates of the alkalies are easily soluble and not crystallizable, the other salts crystallize in shining crystalline scales.

a. Baldrianate of barium crystallizes either in transparent prisms which disappear at 20° to 25° C., or more frequently in plates similar to those of cholesterin, which are readily soluble in water, but difficultly soluble in alcohol. This salt contains 40.41 per cent. of barium.

b. Baldrianate of silver crystallizes in fine plates which shine like silver, and are difficultly soluble. It contains 51.67 per cent. of silver.

*Detection of the Fatty Acids.* To separate the volatile fatty acids, as large an amount of urine as possible must be used. It is strongly acidulated with phosphoric acid, and then distilled as long as the distillate shows any traces of an acid reaction. If the residue in the retort becomes too concentrated, it is allowed to cool, water is added, and the distillation commenced anew. The different distillates are then united, saturated with carbonate of sodium, and evaporated to dryness. The residue is extracted with absolute alcohol, filtered, the filtrate evaporated to dryness, and the saline residue now obtained after the

addition of phosphoric acid, is subjected to distillation as long as the fluid which passes over has an acid reaction. The distillate is first tested with nitrate of silver or mercuric chloride for formic acid. If this is present, it is destroyed by boiling with mercuric oxide, the fluid is saturated with carbonate of sodium, filtered, evaporated, and allowed to stand for a time to crystallize. If acetic acid is present, the acetate of sodium soon crystallizes, as, for example, in old diabetic urine, from which it separates abundantly, and is easy to recognize as such. If the acetate of sodium has separated, the mother liquor is acidulated again with phosphoric acid and subjected anew to distillation. The distillate which is now obtained is treated with baryta water in excess, carbonic acid is conducted into it until it has a neutral reaction, it is heated to boiling, filtered, and evaporated to a small volume for crystallization. The propionate of barium is the most soluble of the barium salts, the butyrate is the least soluble. Analysis of the barium salt obtained will give information of the nature of the acid if only one of the higher members is present, but if several are present at the same time, several barium salts must be obtained by fractional crystallization, and the amount of barium contained in each must be determined, since the material at hand would probably never suffice for producing the different acids in a state of purity.

In using large amounts of urine benzoic acid also is almost always obtained in the distillate, due to the decomposition of the hippuric acid. It separates especially during the second distillation in crystalline plates, which remain partly adhering to the condenser and partly floating on the surface of the distillate, and can readily be recognized as such.

### § 32. BENZOIC ACID.

Formula : $C_7H_6O_2$ $C_{11}H_8O_4$	{	Carbon	68·85
		Hydrogen	4·92
		Oxygen	26·23
		<hr/>	
			100·00

*A. Presence.* Benzoic acid occurs in the urine of herbivora probably after hard work or after wretched fodder. It is formed

constantly in the putrefying urine of these animals, as well as in that of human beings, where it is formed by the decomposition of hippuric acid. Benzoic acid is the non-nitrogenous component of hippuric acid, for, as we have seen above, benzoic acid in the economy takes up the elements of glycoll and appears again in the urine as hippuric acid. Conversely hippuric acid in contact with putrefying matters is decomposed immediately into benzoic acid and glycoll again. Moreover, benzoic acid occurs as a product of the decomposition of many animal substances, especially protein bodies, gluten, etc. Hilger found in the urine passed after partaking largely of asparagus, benzoic acid together with hippuric acid, succinic acid, and an increased amount of ammonium salts.

**B. Microscopic Properties.** Sublimed benzoic acid appears in the form of colorless, fine, shining needles and leaflets, while that obtained from its solutions is in scales, small prisms, or six-sided needles, whose primitive form is a right rhombic prism. On cooling aqueous solutions, the crystals appear under the microscope always connected together, sometimes also in tables of exactly  $90^\circ$  overlapping each other; in rare cases, one angle becomes truncated, but in such a way that the two angles are  $135^\circ$ . (Funke, Taf. I., fig. 6; 2<sup>e</sup> Aufl., Taf. II., fig. 6.)

**C. Chemical Properties.** At  $240^\circ$  C. benzoic acid sublimes undecomposed, its vapors irritate the throat and excite coughing. It is difficultly soluble in cold water, more easily in hot water; alcohol and ether take it up with tolerable ease. Its solutions redden litmus. Benzoic acid volatilizes with aqueous vapor; therefore, only neutral solutions can be concentrated by evaporation.

1. The benzoates are mostly soluble in water, only those of the heavy metals are difficultly soluble. The alkaline benzoates dissolve in alcohol.

2. Strong acids decompose benzoates when in solution with the separation of benzoic acid in white shining scales.

3. Chloride of iron gives in a solution of alkaline benzoates a brownish-yellow precipitate of benzoate of iron, which is decomposed by ammonia with the separation of ferric hydrate and formation of benzoate of ammonium. Benzoate of iron treated with a little hydrochloric acid dissolves with the separation of benzoic acid.

4. Free benzoic acid in a mixture of alcohol, ammonia, and chloride of barium solution, causes as little precipitation as the alkaline benzoates. (Distinction from succinic acid.)

5. If benzoic acid is evaporated with a little nitric acid by boiling in a small porcelain dish, an odor of bitter almonds or nitrobenzol is evolved when the residue is strongly heated.

D. *Detection.* The neutralized urine is evaporated to the consistence of an extract, and this is extracted with alcohol; after evaporation of the alcohol, benzoic acid separates in crystalline form on the addition of a stronger acid. If its amount is very small, so that no crystals are obtained in this manner, the mass is extracted with ether which is then left to spontaneous evaporation; benzoic acid is separated from the ethereal extract in a crystalline form by water. The crystals are examined chemically and microscopically. If succinic acid should be present at the same time, the acids are converted into their barium salts, and these are treated with boiling alcohol. Succinate of barium thus remains behind undissolved, while benzoate and any hippurate of barium present are dissolved. Benzoate of barium remains after evaporating the hot filtered alcoholic solution, and the benzoic acid is readily separated from this by hydrochloric acid. If hippuric acid is present, it can be easily separated by treating with ether, which dissolves the benzoic acid very readily.

If, moreover, decomposed urine is treated as given under the head of Detection of the Volatile Fatty Acids, § 31, at the end of the second distillation, especially when it is pushed a little further, white scales and leaflets will be observed, which for the most part remain in the condensing tube, and are readily recognized as benzoic acid.

### § 33. FATS.

A. *Presence.* Urine containing fat is not a very frequent appearance. The peculiar milky urine which sometimes occurs (*urina chylosa*), frequently owes its cloudiness and color not to fat which is in suspension, but, as Lehmann declares, to a large number of pus corpuscles; but Beale records a case of milky urine abounding in fat which was passed for months in the morning by a woman fifty years old. This urine became per-

fectly clear after shaking with ether. Quantitative estimation showed in 1,000 parts 13.9 grams of fat. Beale believes that the chylous character arose from a separation of chyle by the kidneys. Beale found cholesterin also in the fatty cells passed with the urine in fatty degeneration of the kidneys, which, dissolved in other fats, could be obtained by first extracting with alcohol and subsequent crystallization. Galacturia appears to occur with special frequency in certain tropical regions. A series of cases is recorded in Schmidt's Jahrbuch, 1863, 12, p. 274.

Eggel\* records a similar case of chyluria. 390 cc. of this urine resembling milk yielded to ether 2.68 grams of fatty substance, in which the fatty acids, that is, neutral fats, cholesterin (?) and lecithin or the products of their decomposition, neurin and phosphoric acid, were detected.

*B. Microscopic Properties.* Free fat is readily recognized under the microscope. With regard to the fat drops, they appear as flat disks, which possess a very great refractive power; they have dark, tolerably irregular contours. The single drops are frequently seen under the microscope to flow together, whereby they may be distinguished from fat cells which are perfectly spherical. Fat cells have a round, smooth, sometimes polyhedral form from mutual pressure. The surface also has a strong refractive power; with transmitted light the contours are sharp and dark, but when examined by reflected light the borders appear shining like silver and the centre of the cells is whitish. It is easy to burst such cells by pressure, their contents then flow out, and the surface assumes a more or less wrinkled appearance. (Funke, Taf. VII., fig. 3 und 4; 2<sup>te</sup> Aufl., Taf. XIV., fig. 3 und 4.)

*C. Detection.* Since fat occurs in urine only rarely, and also only in very small amount, we naturally do not think of a separation and individual recognition of the different compounds, and must content ourselves with finding and recognizing it as such. The microscopic appearance is so characteristic and significant that every one who has once seen a fat drop will recognize it again at the first glance. Our first attempt, therefore, is always to recognize under the microscope the

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\* Centralblatt f. d. med. Wissenschaft., 1870, p. 121.

above-mentioned qualities. If this does not succeed, a portion of the urine is evaporated to dryness on the water bath, the residue is exposed for a time to a temperature of  $110^{\circ}$  C., and is treated with successive small portions of ether as long as this takes up anything. This ethereal solution will now contain all the fat, and will leave it behind on evaporation, which is best performed in a small cylindrical glass. The residue can then be tested first microscopically and then chemically, as far as the material suffices. The production of greasy spots on fine paper, as well as the behavior on being heated (development of acrolein), does not admit of a confusion with any other body.

Chylous urine for the most part contains, in addition to greater or less amounts of fat, which is held in the form of an emulsion by the albumen present at the same time, lymph and blood corpuscles. A creamy layer frequently collects on the surface, and after a shorter or longer time fermentation occurs, when fibrinous coagula soluble in a solution of nitre separate. These fibrinous coagula are either delicate white, and fill the whole fluid, or they form clumps of a light or dark red color, sometimes dense, sometimes delicate and mucus-like, which are also soluble in nitre.\*

#### § 34. SULPHURETTED HYDROGEN.

Sulphuretted hydrogen sometimes occurs in the urine, but only in rare cases. Its presence is readily recognized by the fact that a piece of paper moistened with a sugar of lead solution is blackened. The experiment is best performed in the following manner: A small beaker is half filled with the urine to be tested for sulphuretted hydrogen, and it is then covered with a watch glass, on the lower surface of which a small piece of lead paper has been fastened by moistening with a drop of water. According to the amount of sulphuretted hydrogen present, the paper will soon become brown or black, especially if the urine is slightly warmed. Sulphuretted hydrogen is also easily recognized by its stinking odor like that of rotten eggs. I have had the opportunity here of observing a specimen of urine which contained sulphuretted hydrogen for

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\* Schmidt's Jahrbücher, 1863, 12, p. 278.



a long time, and which was passed periodically by a man whose lower extremities were paralyzed by gout; the urine, when it contained sulphuretted hydrogen, was feebly acid, of bright yellow color, usually deposited a sediment, and immediately blackened very intensely a lead paper held over it.

Betz assumes that under certain circumstances sulphide of ammonium from the intestine may get into the blood and then cause symptoms of poisoning, which are similar to those caused by the inhalation of sewer gas. Betz calls the sickness thus caused hydrothion-ammonæmia; in the cases described by him the freshly passed urine gave for a long time the reactions of ammonia and sulphuretted hydrogen.\*

It has been intimated above, under the head of Sulphuric Acid (§ 15, B, 3), that sulphates in contact with organic matters at a moderately elevated temperature may easily give rise to the formation of sulphuretted hydrogen, which is one source of this body in the urine. But sulphuretted hydrogen may be generated also without the presence of sulphates, by the simple putrefaction of animal matters containing sulphur, and thus it may happen that sulphuretted hydrogen can frequently be recognized by its odor in a urine which contains albumen after standing a short time, as I have had frequent opportunity of observing.

E. Sertoli,† moreover, gives an account of a body precipitable by sugar of lead, soluble in ammonia, alcohol, and ether, decomposing with the evolution of sulphuretted hydrogen on being heated with dilute acids to 100° C., and which was found by him in the urine of horses, dogs, and human beings. It is easy to become assured of the presence of a body in the urine which contains sulphur, since the urine of men, horses, and dogs develops, on being treated with zinc and hydrochloric acid, sulphuretted hydrogen, which can be detected by the blackening of a strip of paper moistened with sugar of lead solution. For the quantitative estimation of the sulphur in the urine, which is not present in the form of sulphates, but in the form of this body which furnishes sulphuretted hydrogen, the following method may be adopted: The uric acid is

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\* Betz *Memorabilien*, 1864, p. 146.

† Dall' *Istituto fisiolog. di Pavia*, 1869.



precipitated from the urine of healthy persons and the filtrate divided into two equal parts. In one half the sulphuric acid is directly estimated, in the other after it has been heated with hydrochloric acid and chlorate of potassium till chlorine is developed. From the difference in the amounts of sulphuric acid of the two estimations the amount of sulphur which was originally present not as sulphate is obtained. A twenty-four hours' amount of urine which was 1,500 cc. gave 0.156 gram of sulphuric acid as the product of oxidation of the sulphur contained in the sulphur compound. (W. Löbisch.)\* Finally it is to be remarked that Schmiedeberg† and Meissner‡ have detected hyposulphurous acid as an almost constant constituent of the urine of cats and a very frequent constituent of the urine of dogs.

### § 35. ALLANTOIN.

Formula : $C_4H_6N_4O_3$ [ $C_3H_5N_4O_6$ ]	{	Carbon	30.38
		Hydrogen	3.80
		Nitrogen	35.44
		Oxygen	30.38
			<hr/>
			100.00

**A. Presence.** Allantoin is found in the allantois fluid of the cow and in the urine of young calves as long as they are suckled or fed with milk. It is further found in the amniotic fluid, and in the urine of newborn children within the first eight days after birth. Städeler found it in the urine of the dog when there was disturbance of the respiration; Meissner and Joly also found it in dogs, together with succinate of sodium, after a continuous diet abounding in fat; Köhler found it in the urine of the rabbit after the injection of oil into the lung. Schottin found it finally in human urine after large amounts of tannic acid had been taken. Allantoin is formed from uric acid by treating it with lead peroxide, ferrocyanide of potassium, or permanganate of potassium.

**B. Preparation.** Uric acid is mixed to a thin paste with

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\* Sitzungsbericht d. wien. Acad., Band 63, II.

† Archiv d. Heilk. 1867, p. 422.

‡ Zeitschrift für rat. Med. 1868, Band 81, p. 322.

water, heated to boiling, and lead peroxide is added in small portions until the brown color of the latter no longer disappears. Allantoin separates from the filtrate on cooling in beautiful crystals, while urea remains dissolved in the mother liquor.

C. *Microscopic Properties.* Allantoin appears under the microscope in perfectly clear, shining, colorless, prismatic crystals of a rhombic form, which, when obtained from concentrated solutions, unite into star-shaped rosettes. (Funke, Taf. V., fig. 4; 2<sup>e</sup> Aufl., Taf. III., fig. 4.)

D. *Chemical Properties.* Allantoin has no taste and does not act on vegetable coloring matters; it is soluble in 160 parts of cold water, more readily soluble in hot water. Hot alcohol also takes it up, but it separates again for the most part on cooling. It is insoluble in ether.

1. Concentrated alkalies decompose allantoin with absorption of water into oxalic acid and ammonia.

2. Boiling nitric acid splits it up into urea and allantoic acid.

3. If nitrate of silver and ammonia are added to a saturated solution of allantoin, allantoin silver oxide precipitates in white flakes which, when examined microscopically, are seen to consist of clear perfectly spherical globes. The dry compound contains 40.75 per cent. of silver.

4. Corrosive sublimate does not precipitate a solution of allantoin, but it is precipitated like urea by a solution of mercuric nitrate.

5. Allantoin in contact with yeast at a temperature of 30° C. is decomposed into urea and oxalate and carbonate of ammonium. At the same time a new syrupy acid is formed, which is, perhaps, identical with one which I observed together with allantoin and urea after treating uric acid with permanganate of potassium.

E. *Detection.* To find allantoin the urine is precipitated with basic acetate of lead, filtered, and the excess of lead removed from the filtrate by sulphuretted hydrogen. The filtered solution is evaporated to dryness on the water bath, and the residue extracted with boiling dilute alcohol. After the cooling of the filtrate, concentrated by evaporation if necessary, if allantoin is present, crystals shoot forth which, after recrystallization from hot water, are to be further examined. Besides

the microscopic forms of pure allantoin, allantoin silver oxide (D, 3) is especially characterized under the microscope by its peculiar globular form. According to Meissner the following method is to be pursued: The urine is precipitated with baryta water, the excess of baryta is carefully removed with sulphuric acid avoiding an excess of the latter, and the alkaline filtrate treated with concentrated corrosive sublimate solution as long as a precipitate results. The mixture, which has now become acid, is neutralized with potassic hydrate, and further treated with corrosive sublimate solution. The collected precipitates are suspended in water and decomposed by sulphuretted hydrogen. Allantoin separates from the concentrated filtrate in crystals. The allantoin which is obtained is best crystallized once more from hot water, before the microscopic examination and production of the characteristic silver compound.

The urine of young calves is evaporated to a syrup on the water bath and placed at rest for several days. The separated crystals are washed and then heated to boiling with a little water. The solution is decolorized by animal charcoal, filtered while hot, treated with a few drops of hydrochloric acid to prevent the separation of phosphate of magnesium, and allowed to cool, when allantoin will separate in thin bundles of coalescing crystals.

The urine of calves, unlike that of full-grown creatures which no longer live on milk, is strongly acid; it contains as much urea and uric acid as human urine, but no hippuric acid, while, on the other hand, cow's urine, which abounds in hippuric acid, contains no allantoin.

## APPENDIX.

*Alloxan.* This interesting product of oxidation of uric acid (§ 6, D, 6 and 7) has thus far been found only once by Liebig\* in a catarrhal intestinal mucus, and again probably by G. Lang† in the urine of a patient with heart disease.

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\* *Annalen d. Chem. u. Pharmacie*, Band 121, p. 80.

† *Centralblatt f. med. Wissenschaft.*, 1867, p. 63. *Zeitschrift f. analyt. Chem.*, Band 6, p. 294.

## § 36. LEUCIN.

<b>Formula :</b> $\text{C}_6\text{H}_{13}\text{NO}_2$ $[\text{C}_{12}\text{H}_{13}\text{NO}_4]$	{	<b>Carbon</b>	<b>54.96</b>
		<b>Hydrogen</b>	<b>9.92</b>
		<b>Nitrogen</b>	<b>10.68</b>
		<b>Oxygen</b>	<b>24.44</b>
			<hr/>
			<b>100.00</b>

A. *Presence.* Leucin was first obtained as a product of the decomposition of animal matters abounding in nitrogen as well by their putrefaction as by the action of strong acids and alkalies upon them, but very recently it has been recognized as a normal and pathological constituent of various organs and fluids of men and animals, in which it often occurs jointly with tyrosin. According to the recent investigations of Radziejewsky\* leucin occurs normally in the pancreas, in the spleen, the lymph glands, salivary glands, in the thyroid and thymus glands and in the liver; in the kidneys it is doubtful. It does not occur in the testicles, lungs, heart and other muscles, in the brain, blood, urine, saliva or bile. Leucin occurs pathologically in the urine in several diseases, typhoid fever, small-pox, hepatic diseases, and is especially abundant together with tyrosin in acute atrophy of the liver. V. Gorup-Besanez found leucin with asparagin in the juice of the embryo of the common vetch (*Vicia sativa*).

B. *Microscopic Properties.* Impure leucin, as it is first obtained by separation from animal fluids, crystallizes in granular masses, which appear as round spheres, mostly yellow, in part concentrically striped, here and there also covered with fine points, yet under the microscope showing no definite crystalline form, but frequently rather reminding one of spherical fat-cells. In the pure state it crystallizes in rosettes of leaflets or scales, whose contour is often difficult to distinguish. More frequently the edges are seen as sharp dark lines, so that at the first sight several crystals appear only as needles fine as hairs which terminate in two points. (Funke, Taf. III., fig. 6; 2<sup>o</sup> Aufl., Taf. IV., fig. 2.)

C. *Chemical Properties.*—1. Pure leucin forms white crystalline

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\* Archiv f. patholog. Anat., Band 86, p. 1, auch Zeitschrift f. analyt. Chem., Band 5, p. 466.

scales, has a greasy feel, and has neither taste nor odor. Water moistens it with difficulty, but dissolves it with tolerable readiness; in alcohol it is more difficultly soluble; it is not at all soluble in ether. Acids and alkalies take it up with ease.

2. Cautiously heated in a glass tube, open at both ends, to about  $170^{\circ}$  C., leucin sublimes without previously melting in woolly flocculent masses, which fly about in the air like oxide of zinc partially borne along by the current of air. This interesting sublimation is very characteristic of leucin. On being strongly heated,  $180^{\circ}$  C., it melts and is decomposed into carbonic acid and amylamin.

3. If a boiling mixture of leucin and sugar of lead solution is carefully treated with ammonia, leucin lead oxide separates in beautiful iridescent leaflets.

4. A solution of mercuric nitrate does not precipitate a solution of absolutely pure leucin. If a precipitate is thus produced, it indicates, especially if the supernatant fluid is colored reddish or rose red, an admixture with tyrosin.

5. Leucin in contact with putrefying animal matters or on being fused with potassic hydrate decomposes, with the formation of carbonic acid, ammonia and hydrogen, into baldrianic acid.

6. If pure leucin is carefully evaporated with nitric acid on platinum foil, a colorless, scarcely perceptible residue remains. If a few drops of sodic hydrate are added to this residue and heated, the leucin thus treated dissolves according to its purity to a perfectly colorless or more or less colored fluid. If this is carefully concentrated on the platinum foil over the lamp, in a short time it collects into an oily drop, which does not wet the platinum foil but rolls about without adhering to it. This appearance is very characteristic even for leucin not wholly pure. (Scherer.)

7. Leucin in alkaline solution is decomposed by permanganate of potassium into ammonia, carbonic acid, oxalic acid, and baldrianic acid.

8. If leucin is heated in a test tube with manganese dioxide and dilute sulphuric acid, the characteristic odor of valeronitrile is developed; and if the oxidation is carried farther, especially if concentrated sulphuric acid is used, that of valerianic acid.

D. *Preparation and Detection.* (See under Tyrosin.)

## § 37. TYROSIN.

Formula : $C_9H_{11}NO_3$ [ $C_{10}H_{11}NO_3$ ]	{	Carbon	59·67
		Hydrogen	6·08
		Nitrogen	7·73
		Oxygen	26·52
		<hr/>	
			100·00

A. *Presence.* Tyrosin is formed in just the same manner as leucin, only a little later, but for the most part together with it during the decomposition of animal matters abounding in nitrogen. Tyrosin never occurs normally in the organism, according to the thorough investigations of Radziejewsky,\* but it does occur in the liver, in the blood of the hepatic and portal veins in diseases of the liver, in the bile of typhoid-fever patients, in the expectoration in croupous bronchial affections, etc. Leyden found it in the expectoration of a girl who had suffered ten years from a cough. It has been found in the urine in typhoid fever and small-pox, and in large quantity together with leucin in acute atrophy of the liver. (Frerichs, O. Schultzen, and L. Riess.)

B. *Microscopic Properties.* Tyrosin forms a cohesive, snow-white mass which has a silky lustre and consists of long shining needles lying together, which again are themselves formed of very fine needles arranged in star-shaped groups. It crystallizes from an ammoniacal solution often in globules, which consist of a number of fine needles radiating from the centre, and appear toothed on the entire periphery by the projection of small pointed crystals over the edge of the sphere. Such a tyrosin sphere on being crushed under the covering-glass crumbles into fragments which consist of very fine white needles. (Scherer.) (Funke, 2<sup>te</sup> Aufl., Taf. IV., fig. 3.)

C. *Chemical Properties.* Tyrosin is without taste and odor, very difficultly soluble in cold water, easily in hot, still more easily in acids and alkalies, but insoluble in alcohol and ether.

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\* Loc. cit.

1. It evolves the odor of phenol and nitrobenzol on being heated. (Kühne.) It is not capable of sublimation.

2. Nitric acid evaporated carefully with tyrosin yields besides oxalic acid a yellow body which is the nitrate of nitrotyrosin; this residue becomes colored a deep red-brown by potassic hydrate and ammonia. If tyrosin is evaporated with nitric acid (sp. gr. 1.2) on platinum foil, the rapidly soluble tyrosin becomes colored bright orange-yellow when first touched by the hot nitric acid. On evaporation it leaves a shining, transparent, deep yellow residue, and if a few drops of sodic hydrate are added to it, the fluid immediately becomes colored deep reddish yellow and on evaporation leaves an intense blackish-brown residue. Scherer prefers this reaction even to Piria's (4), because of its easy performance.

3. If a boiling solution of tyrosin is treated with a solution of neutral mercuric nitrate, obtained by treating an excess of mercuric oxide with nitric acid, a yellowish-white voluminous precipitate results. If then a few drops of fuming nitric acid mixed with a large amount of water are added drop by drop to the fluid to be examined, which is allowed to boil anew after the addition of each drop, the whitish precipitate immediately becomes dark red. If the amount of tyrosin is very small, the fluid, which was before only turbid, like milk, becomes pale red, and after a time dark-red flocculi are deposited, while the fluid becomes colorless. (L. Meyer.)

4. If a few drops of concentrated sulphuric acid are poured over tyrosin in a porcelain dish, it dissolves, on being gently heated, with a transitory red color. If then, after diluting with water, the acid is neutralized with a milk of carbonate of barium, boiled to destroy the bicarbonate of barium, and a dilute *neutral* solution of ferric chloride carefully added to the filtrate, a beautiful violet color is produced. No great amount of leucin should be mixed with the tyrosin. This reaction is very delicate; the color appears bright rose-red in an ordinary test tube at a dilution of 6,000, in a layer two inches thick a distinct rose-red color is observed at a dilution of 25,000, and in one eight inches thick at a dilution of 45,000. (Piria, Städeler.)

D. *Preparation.* Two pounds of horn shavings are treated with a mixture of five pounds of English sulphuric acid and thirteen pounds of water, and boiled twenty-four hours consec-



utively, the water evaporated being renewed. The sulphuric acid is then removed by milk of lime, the mixture filtered, washed with hot water, and the filtrate, after the solution has been concentrated to about twelve pounds, is freed from dissolved lime by the careful addition of oxalic acid. The filtrate is evaporated until a crystalline pellicle forms. The rosettes of crystals obtained consist of leucin with varying amounts of tyrosin, which is seldom absent. The different solubility of the two substances in water is utilized to separate them; for this purpose they are dissolved in so much boiling water that on cooling only a small part of the crystals separate, which consist of white needles of the difficultly soluble tyrosin. Leucin is obtained from the mother liquor after previous decolorization with animal charcoal and further evaporation in white masses of crystals.\*

The following method of W. Kühne† is an excellent one: The pancreas of a well-nourished animal which has been abundantly fed five or six hours before death, is weighed while fresh, cut into pieces, triturated with water and sand to a fine mush, ten times its amount of raw blood fibrine is added, and the whole treated with twelve or fifteen parts of water, which should be previously warmed with the fibrine to 45° C. The mass is kept at this temperature with frequent stirring for four or five hours, then a little acetic acid is added, and it is heated to boiling. It is then strained through linen, the fluid is evaporated to a thin syrupy consistency, and while still hot is treated with strong alcohol and shaken in a flask until a distinct flocculent precipitate results. After cooling, this is filtered, and the filtrate is concentrated by evaporation until it forms a thick pulp when hot. After the mass has stood a day in the cold, it is freed as much as possible from the mother liquor on a filter, washed with a little cold water and then suspended in considerable water at about 50° C., when all of the leucin is dissolved while the tyrosin remains behind nearly white. It is first recrystallized from hot water to purify it, and then from hydrochloric acid or ammonia to obtain large crystals.

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\* Schwanert über Leucin; Dissertation, Göttingen, 1857. Städelers. Annal. der Chemie und Pharm., Band 116, p. 61.

† Archiv f. path. Anat., Band 39, p. 130. Zeitschrift f. analyt. Chemie, Band 6, p. 282.



*E. Detection.* In acute atrophy of the liver under certain circumstances only traces of those substances occurring normally as the final product of metamorphosis, especially urea, are found, while leucin and tyrosin occur as the principal constituents. Such a urine often deposits a greenish-yellow sediment spontaneously, consisting of spherical rosettes of tyrosin needles, and leaves a residue of numerous crystals of both substances when it is evaporated on an object glass. To obtain larger amounts of both bodies Frerichs freed such a urine from the coloring and extractive matters, as it also gave distinct reactions for biliary pigments, by precipitating it with basic acetate of lead, immediately after obtaining it, with a catheter; he then filtered, precipitated the excess of lead from the filtrate by sulphuretted hydrogen, and concentrated the clear fluid. After twenty-four hours a sufficiently large amount of tyrosin had separated to suffice for several elementary analyses.\* The tyrosin obtained is recrystallized from hot water and the chemical and microscopic tests are applied to it. To find leucin the evaporated residue is next treated with cold absolute alcohol, as long as it takes up anything, and it is then extracted with boiling alcohol of ordinary strength, when a substance remains behind for the most part viscid, dark brown, soluble in water, and containing the remainder of the tyrosin. The alcoholic solution last obtained is evaporated and the syrupy residue allowed to stand a long time, when any leucin present separates in the globular form described above, § 36, B, and is to be subjected to microscopic and chemical examination. It is better, having first as much as possible freed the leucin obtained from its mother liquor by pressing between paper, to further purify it; for which purpose its compound with lead oxide may be utilized. The aqueous solution of the leucin, which has been purified as much as possible by pressure, is made strongly alkaline with ammonia for this purpose and then precipitated with acetate or basic acetate of lead solution as long as a precipitate results. The precipitated leucin lead oxide is collected on a filter, washed a little, then suspended in water and decomposed with sulphuretted hydrogen. The fil-

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\* Together with tyrosin still another body crystallizing in a similar form was found, which contained more nitrogen (8.83 per cent.). Frerichs, *Deutsche Klinik*, 1855, Nr. 31, p. 343.

trate after evaporation will separate the leucin in pure crystalline form. (Lehmann.) If the urine should contain albumen, it is first coagulated by heat, and the filtrate used for testing for leucin and tyrosin.

It is to be remarked further that such a urine is to be examined while fresh, since leucin in contact with decomposing animal matters is very readily decomposed with the formation of baidric acid.

The urine from the case of acute atrophy of the liver, described by Frerichs, contained 4.9 per cent. of solid residue and 0.14 per cent. of ash. The residue was strongly acid, and urea was sought for in it in vain. He obtained, besides leucin and tyrosin, a viscid substance, similar to that which is formed with leucin and tyrosin by the artificial decomposition of protein substances by acids. The ash consisted chiefly of chlorine compounds and sulphates; it was remarkable that the alkaline and earthy phosphates were wholly wanting. These statements were partially confirmed by O. Schultzen and L. Riess.\*

### § 38. OXYMANDEL ACID.

Formula : $C_9H_8O_4$ [ $C_{10}H_8O_5$ ].	Carbon	57.14
	Hydrogen	4.76
	Oxygen	38.10
		<hr/> 100.00

*Presence.* Oxymandel acid was found by O. Schultzen and L. Riess† in the urine in several cases of acute atrophy of the liver, together with leucin, tyrosin and paralactic acid. The urine, moreover, contained biliary pigments, biliary acids, small amounts of albumen, and that peptone-like substance which often occurs in the urine after phosphorus poisoning in considerable amount (page 100). The urea was either wholly wanting or was reduced to a minimum. Leucin and tyrosin were never absent, so that these bodies may be regarded as almost as pathognomonic of acute atrophy of the liver, as albumen is of nephritis and sugar of diabetes mellitus.

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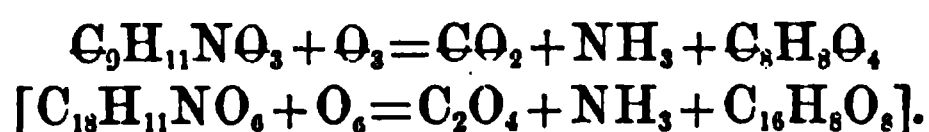
\* Loc. cit.

† Ueber acut. Phosphorvergiftung und Leberatrophie, Berlin, 1869, p. 69.

*B. Detection and Properties.* The urine was freed from its tyrosin and leucin by evaporation, the mother liquor was precipitated with absolute alcohol, the alcoholic solution evaporated, and the syrupy residue after the addition of dilute sulphuric acid completely exhausted with ether. The united ethereal extracts on evaporation left a brown, thin, fluid residue, from which long, thin colorless needles, together with brown oily drops, separated. On treating with water the latter dissolved. Sugar of lead solution caused only a slight flocculent precipitate in the slightly yellow fluid, by which means it was decolorized. Basic acetate of lead gave with the clear, watery filtrate an abundant flocculent precipitate, which, after standing a short time, condensed to a heavy, granular, crystalline powder. The compound was suspended in water and decomposed with sulphuretted hydrogen. The filtrate yielded, after evaporation, colorless, very flexible silky needles of the new acid.

In a pure state oxymandel acid melts at  $162^{\circ}$  C.; it contains water of crystallization which escapes when exposed to the air at  $130^{\circ}$ . It is quite soluble in warm water, less so in cold water, and readily soluble in alcohol and ether. On heating in a glass tube with calcic hydrate brown oily drops appeared which had the odor of phenol, and in an aqueous solution gave a dark violet color with ferric chloride.

The simultaneous occurrence of tyrosin and of oxymandel acid in the urine, from the chemical relationship of the two substances, allows us to suppose that the latter springs from the former. This change may be expressed in the following formula:



By a similar method O. Schultzen and Riess\* obtained from the ethereal extract of urine in acute phosphorus poisoning warty groups of delicate, colorless, rhombic leaflets of a new aromatic acid. On fusing with potassium it yielded cyanogen, and on distillation with lime anilin. It melted constantly at  $184^{\circ}$  to  $185^{\circ}$  C.; the silver salt contained 33.92 per cent. of silver. Unfortunately the material did not suffice for an accurate investigation.

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\* Loc. cit., p. 87.

## § 39. BRENZCATECHIN.

*(Oxyphenic Acid.)*

W. Ebstein and J. Müller\* found a substance in the urine of a boy four months old, which corresponded with brenzcatechin in all of its properties. The urine, colorless when passed, retained its original color, but if in contact with air, it became first reddish, then gradually darker up to the color of burgundy. On the addition of potassic hydrate the urine became brownish, but later blackish brown, especially on shaking.

*Detection.* Two hundred cc. of the urine in question were evaporated on the water bath, and the residue repeatedly shaken with absolute alcohol. The residue did not become brown as mentioned above; the substance in question had, therefore, been removed by the alcohol completely. The alcoholic filtrate was once more evaporated on the water bath, and the residue repeatedly shaken with ether. After evaporating the ether there remained a yellow syrupy mass, which was treated with small amounts of water in the cold to separate the hippuric acid. This solution gave all of the reactions of brenzcatechin.

1. Evaporated over sulphuric acid on an object glass, white, rectangular, prismatic crystals separated.

2. Alkalies produced a green color in the solution. This became gradually greenish brown, brown, and at last almost black.

3. Silver, gold, and platinum solutions were reduced even in the cold.

4. An alkaline solution of copper was reduced on heating.

5. A solution of ferric chloride immediately produced a color which was first dark green, then black. If, further, tartaric acid was added to a fluid which contained only traces of ferric chloride, the mixture rendered ammoniacal, and then treated with some of the aqueous solution of the body in question, the characteristic violet color was produced, which changed on the addition of acetic acid to a faint green, becoming violet again after the addition of ammonia.

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\* Virchow's Archiv, Band 62, p. 554.

6. Acetate of lead gave a white precipitate soluble in acetic acid.

Although, on account of dearth of material, the sublimation test and the elementary analysis could not be performed, yet the reactions given correspond so completely with those of brenzcatechin, that scarcely any doubt exists as to the presence of this remarkable substance in the urine in question. In many respects also the urine corresponded with that in which Bödecker found alkapton (p. 114), which was possibly brenzcatechin also.

Finally it must be mentioned that V. Gorup-Besanez found brenzcatechin in the leaves of the wild vine (*Ampelopsis hederaea*), and Hoppe-Seyler recognized it as a product of the decomposition of starch, cane sugar, sugar of milk, and cellulose, after heating these substances from four to six hours with water in sealed tubes to from 200° to 280° C.

#### § 40. URORUBROHÆMATIN AND UROFUSCOHÆMATIN.

These two well-characterized pathological coloring matters, which appear to stand in close connection to hæmatin, were found by F. Baumstark\* in the urine of a patient suffering with leprosy. The color of the urine was at first a deep dark red, like Bordeaux wine, and gradually became brown red and toward death a pure dark brown, almost black.

*Preparation.* The urine was subjected to dialysis, when a yellow-colored fluid like normal urine passed through the membrane with the salts, while a brown slimy substance remained behind. This readily dissolved in sodic hydrate from which the addition of an acid precipitated the urofuscohæmatin, while a beautiful magenta-red coloring matter, urorubrohæmatin, remained in solution. The latter separated when the red solution was subjected to dialysis. The quantity of the two pigments amounted in twelve days to about two grams.

*Urorubrohæmatin* ( $C_{63}H_{94}N_8Fe_2O_{38}$ ) was obtained as a bluish-black light mass, which is insoluble in water, alcohol, ether, and chloroform; but is soluble in the fixed alkalies, their carbonates and phosphates, and also in alcohol containing acid.

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\* Berliner Berichte, Band 7, p. 1170. Pflüger's Archiv, Band 9, p. 568.

None of these solutions are dichroic, even after the addition of a zinc salt.

The acid solution shows a narrow absorption band in front of D and a broad one behind D, so that it appears as if the oxyhæmoglobin spectrum were displaced toward the left, yet the bands stand nearer each other than in the oxyhæmoglobin spectrum. On dilution the narrow band disappears first. The alkaline solution shows a band on the right of D, one at E, a broad one right of F, and one to the right of G, without the blue being absorbed between the two last; all four bands diminish uniformly on dilution.

*Urofuscohæmatin* ( $C_{68}H_{108}N_8O_{16}$ ) is a black, pitchy, shining mass with a similar behavior with solvents as the red coloring matter. The solutions are not dichroic. In the spectrum a shadow appears between D and E, and a second one in front of F, which can only be recognized with difficulty.

In both coloring matters the proportion of carbon to nitrogen is as 8 to 68, as in hæmatin; both yield on dry distillation a distillate, which like the hæmatin derivatives investigated by Hoppe-Seyler show the pyrrol reactions very beautifully. Hæmin crystals cannot be produced from the coloring matters.

#### § 41. ACETONE, ALCOHOL, AND ETHYLDIACETIC ACID.

F. Rupstein\* found acetone and alcohol in the urine of a woman forty years old suffering from severe diabetes. The breath of this woman had an odor of chloroform, which was not noticed in the freshly passed urine, but which became very striking after a few hours.

*Detection.* During six weeks the urine which was passed was daily subjected to distillation, and the distillate after the addition of sulphuric acid was repeatedly subjected to fractional distillation. The product obtained on the fourth distillation had a repugnant urinous odor only slightly resembling that of acetone, but it was inflammable, did not mix with sodic hydrate, by which it was blackened just as by sulphuric acid, and gave a crystalline precipitate with a drop of a concentrated solution of acid sodium sulphite (characteristic reaction for aldehyd and acetone). The first fraction of this fluid distilled at 67°

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\* Centralblatt f. d. med. Wissenschaft., 1874, Nr. 55.

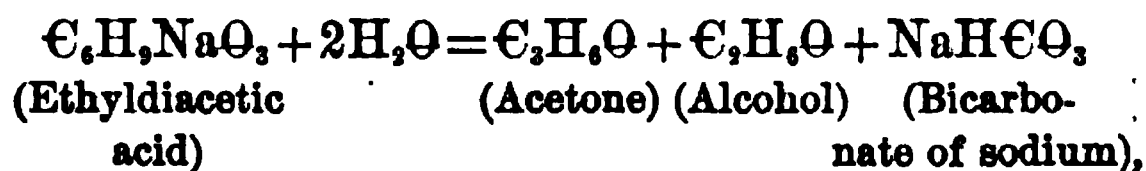
C. The distillate was treated with fused chloride of calcium, then distilled on the water bath, and the distillate once more subjected to similar treatment. That which now volatilized at 60° C. (40 cc.), which had an odor of acetone, was once more distilled in small portions over the water bath, and the portion which passed over at 58° C. was employed for the elementary analysis.

Further heating of the chloride of calcium residue over a free flame yielded a fluid consisting essentially of ethyl alcohol. The alcohol was converted into acetic ether, and this after repeated rectification submitted to analysis.

*Derivation of Acetone and Alcohol.* Gerhardt first laid stress on the fact that a diabetic urine in which acetone is contained or is formed is at the same time characterized by a remarkable reaction, namely, treated with ferric chloride, a deep red-brown color is produced. This reaction corresponds with the demeanor of ethyldiacetic acid discovered by Geuther, which decomposes with great readiness into acetone, alcohol, and carbonic acid.

Since now the freshly passed urine gave the above reaction with ferric chloride, but did not have the odor of acetone, and since the iron reaction disappeared on boiling as well as after long standing, and instead of it the acetone odor appeared, Rupstein supposes that this diabetic urine originally contained ethyldiacetic acid, and that by its decomposition acetone and alcohol were formed. This supposition gains probability from the fact that normal urine treated with ethyldiacetic acid behaves exactly like the above specimen of diabetic urine. Finally Rupstein succeeded in isolating a body from a large amount of this diabetic urine after acidulating it with acetic acid and shaking with ether, which after the addition of an ethereal solution of ferric chloride immediately showed a deep brown color.

Since now alcohol could be detected at the same time in the urine, Rupstein considers that the presence of ethyldiacetic acid in diabetic urine is proved, and by its decomposition according to the formula





acetone and alcohol are first formed with the separation of carbonic acid.

#### IV. URINARY SEDIMENTS.

##### § 42.

The various deposits which occur more or less in every urine, and which are in part passed with it and in part are first separated after a shorter or longer time, are termed urinary sediments. The microscope shows that they consist of organized and non-organized forms, and that the latter are sometimes amorphous and sometimes occur in well-formed crystals. We divide sediments, therefore, into organized and non-organized, and must distinguish the normal which occur in every urine from the pathological sediments. If we leave normal, freshly passed urine a short time at rest in a closed glass, light clouds of mucus are soon observed to sink, which mucus comes from the mucous membrane lining the urinary passages and the bladder, and in which the microscope shows, besides the different forms of epithelium from the urinary passages, etc., isolated mucous corpuscles. Very frequently, often on very slight disturbance of the health, the urine soon after cooling deposits a sediment consisting of fine or coarse molecules, which are easily dissolved again by the application of gentle heat. These consist of a mixture of acid urates, in which, according to the investigations of Bence Jones, urate of potassium, sodium, and ammonium, in feeble combination with an excess of uric acid are never wanting, but with which urate of calcium and magnesium may also be admixed. (Plate II., fig. 1.) In perfectly normal urine so small an amount of urates occurs that they remain in solution a long time after cooling; if, however, the urine is very concentrated, or if an abnormal amount of urates is separated by the kidneys, they are deposited as a sediment very soon after cooling. In most febrile conditions, and under all circumstances in which oxidation in the blood is impeded, the urates appear most frequently as the long-familiar "sedimentum lateritium." We mentioned above, in § 1, that urine on standing very frequently underwent an acid fermentation, which after a shorter or longer time was always followed by



an alkaline one. The urine in the first stage of this decomposition frequently assumes a somewhat darker color, which commences on the surface and gradually and slowly proceeds downward. According to the investigations of Pasteur oxygen is absorbed during this stage, so that this first act of the decomposition of urine must be designated as a process of oxidation. In the alkaline fermentation, on the contrary, the color of the urine becomes gradually paler.

This act of fermentation stands in the nearest relation to the formation and separation of many sediments. If we examine the sediment of urates just spoken of under the microscope, after the acid fermentation of the urine has commenced, we shall find first isolated fermentation spores and in addition mucous coagula in broad or narrow curved bands. (Plate II., fig. 2.) On increasing acidification the appearance becomes changed. The stronger acids are formed, among which may be especially mentioned acetic acid, which is never wanting in old urine, and decompose the urates; the latter decrease, but in their place beautiful rhombic crystals of uric acid appear, which are usually colored yellow, and which are not rarely accompanied by single crystals of calcic oxalate. (Plate II., fig. 4.) The separation of uric acid, however, is not always preceded by a sediment of urates, but very frequently takes place immediately during the stage of acid fermentation in crystals recognizable by the naked eye as a granular sand with a golden lustre.

According to the investigations of Voit and Hofman\* sediments of uric acid may separate without previous fermentation, since the acid phosphate of sodium decomposes the alkaline urates dissolved in the urine with the formation of a basic salt. In fact, if equivalent amounts of the solutions of the two salts are brought together, after a time crystalline uric acid precipitates and the fluid has an alkaline reaction. These facts, according to Voit, completely explain the origin of uric acid sediments. The action of the acid phosphate of sodium on the alkaline urates commences immediately after the formation of acid urine; the urates and then the uric acid are precipitated more rapidly when the urine contains a large amount of acid phosphate. It is self-evident that this precipitation

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\* *Zeitschrift f. analyt. Chemie*, Band 7, p. 397.

may take place even within the urinary passages and bladder, and may thus give rise to the formation of gravel or calculi. This change of the two salts is made more rapid either by a more abundant secretion of acid phosphate of sodium or by a greater concentration of the urine. When the action of the acid phosphate of sodium is rapid, the precipitate is amorphous, and when slow the uric acid separates in the crystalline form. Through this transposition the acid reaction of the urine is gradually diminished, so that an alkaline reaction may easily occur even before the decomposition of the urea, if only just enough acid phosphate of sodium is present to form a basic salt with the sodium in combination with uric acid.

After a shorter or longer time, often only after some weeks, the second act of the decomposition of urine, alkaline fermentation, commences. The urea is then decomposed into carbonate of ammonium, according to Tieghem, by the action of a small torula, which consists of a chain or heap of small spheres without an integument, of about 0.0015 millimeter in diameter, and without nuclei. This vegetable ferment appears to increase by budding, and never develops on the surface of the fluid, but either in its interior or at the bottom of the vessel, where it finally forms a white deposit mixed with the separated salts. As soon as this torula occurs in the urine the decomposition of the urea commences. If infusoria appear at the same time, as is usual, the urea is decomposed more slowly, but if other vegetable productions appear on the surface, by which the development of the torula is hindered, the urine may remain acid for months, according to Tieghem.\* If the alkaline fermentation has commenced, and if the urine has still only a feebly acid or neutral reaction, the sediment has another appearance. The crystals of uric acid gradually dissolve and their rudiments are frequently beset with prismatic crystals of urate of sodium, and here and there with dark spheres of urate of ammonium. When the reaction finally becomes alkaline, uric acid has disappeared, shining crystals of ammonio-magnesian phosphate, and dark, often prickly spheres of urate of ammonium, appear in the sediment, besides a very large amount of amorphous

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\* Concerning the decomposition of urine see also Hallier, "Gährungserscheinungen, etc., etc.," Leipzig, bei W. Engelmann, 1867, and § 52, "Spores and Infusoria."

phosphate of calcium, while the surface of the urine is often thickly covered with mould. (Plate II., fig. 5.)

Under pathological conditions both stages of urinary fermentation may occur in the bladder. If the acid fermentation occurs, uric acid will be separated and will be passed with the urine in the form of coarse or fine gravel. In the alkaline fermentation the sediments mentioned are frequently mingled with large amounts of pus. (Plate II., fig. 3.) We must not leave the fact unmentioned here, that by the use of foul catheters, elastic as well as silver, germs of spores, etc., have been introduced into the bladder, and thus given rise to the alkaline fermentation within the bladder with all of its evil consequences. (Niemeyer and Teuffel, Traube and Fisher.)

Frequently under pathological conditions large amounts of calcic oxalate occur in the sediment; on the other hand, sediments of cystin, tyrosin, xanthin, sulphate of calcium,\* and crystallized phosphate of calcium are rare. Of the organized substances, in addition to the different forms of epithelium, blood and pus corpuscles, renal casts, spermatozoa, and sarcinæ are frequent found pathologically, and under certain circumstances, masses of cancer and tubercle. We will now consider the individual constituents.

#### 1. NON-ORGANIZED SEDIMENTS

##### § 43. URIC ACID.

Uric acid occurs as a sediment only in strongly acid urine, and is frequently accompanied by one of the urates. As a sediment it is never colorless, though at times it is pale yellow, but is usually of a deep-yellow, orange-red, or brown color. Its crystalline character is readily recognized even with the unaided eye, and if we examine it under the microscope, it appears in the forms mentioned above under uric acid, § 6. Four-sided tables or six-sided prisms of rhombic shape, from which often by the rounding of the obtuse angle spindle or barrel-shaped crystals are formed, are characteristic. If, however, there is any doubt about any crystal, it is only necessary

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\* Valentiner, med. Centralblatt, 1863, p. 913.

to dissolve the sediment on an object glass in a drop of potassic hydrate, and to add a little hydrochloric acid, when the usual forms will soon appear. It is separated from the urates mixed with it by heating and filtering; the urates are in solution, while free uric acid will remain behind on the filter. Finally it can be tested chemically, especially by the murexid test, for which very minute quantities of uric acid will suffice. (Plate I., figs. 2 and 3; Plate II., fig. 4; Plate III., fig. 1.)

#### § 44. URATES.

If urates are present in the sediment together with free uric acid, they may be separated by heating, as has been indicated, and after the filtrate has become cool, they separate. The color is very variable grayish white, white, rose red, brown red, or purple red; they often look very much like organized bodies, as blood, pus, etc., and can be distinguished from them only by the microscope; they are, however, readily recognized chemically by their behavior with nitric acid and ammonia (formation of murexid) as well as by their solubility on heating.

Sediments of urates occur most frequently in febrile conditions, and under all circumstances in which the respiration, or rather oxidation in the blood, is interfered with.

Bence Jones has examined the sediments consisting of urates very carefully, and has found that they contain in 100 parts 91.06 to 94.36 per cent. of uric acid, 3.15 to 5 per cent. of potassium, 1.11 to 1.87 per cent. of sodium, and 1.36 to 3.36 per cent. of ammonium. If these precipitates are washed with water on the filter, they frequently show crystals of uric acid under the microscope, and on boiling with water they leave uric acid behind undissolved. From these experiments it is evident that the sediment of amorphous urates often contains far more uric acid than is requisite to form acid salts, and that this excess is held in such feeble combination by the acid salts that cold water sets free crystals of uric acid. Bence Jones succeeded in producing artificially a urate of potassium of similar behavior, which was found, on analysis, to be a fourfold acid salt. It follows from this that the sediment of amorphous urates has no constant composition. It is a mixture of different acid urates, which are modified in their crystalline form by other

substances in the urine. The potassium salt was found for the most part in greater amount than the urate of ammonium or sodium; there is also usually an excess of uric acid in combination with these acid salts, so that by washing with water readily decomposable quadruple urates are formed, by which the sediment is made more susceptible of variation in its composition.

1. *Acid Urate of Sodium* in most cases appears in the form of amorphous, irregular granules of very small size. Produced artificially by dissolving uric acid in a warm solution of ordinary phosphate of sodium, it is obtained in microscopic prismatic crystals which ordinarily unite to form masses grouped in a stellate form. It is found at times in the urine in a similar form after acid fermentation is complete and when alkaline fermentation is just commencing. Microscopic examination of the sediment in this transition stage often shows very complicated forms. The crystals of uric acid separated during acid fermentation and now more or less dissolved are covered with beautiful groups of prismatic crystals of urate of sodium, while at the same time concentrically striped spheres are observed which here and there adhere to the prismatic crystals and probably consist of urate of ammonium. Such a urine still feebly reddens litmus as fermentation progresses, and when a neutral reaction has already resulted, groups of prismatic acid urate of sodium crystals are sometimes seen, but now accompanied by beautiful large crystals of ammonio-magnesian phosphate.

Acid urate of sodium dissolves in water with difficulty; one part requires 124 parts of boiling water, and 1,150 parts of cold water. On the addition of hydrochloric acid crystals of uric acid are separated.

2. *Acid Urate of Potassium* is also frequently found in the sediment of urates, and is similar to the sodium salt in every respect.

3. *Acid Urate of Ammonium*. This sediment occurs chiefly in alkaline urine mixed with the earthy phosphates. Under the microscope it appears in spherical, opaque masses, which are studded with peculiar, fine, prominent points. If a drop of hydrochloric acid is added to it on a glass slide the familiar crystals of uric acid very soon appear. It dissolves in hot water but separates again on cooling. If it is treated with a very little potassic hydrate, ammonia is evolved; with nitric

acid and ammonia it gives the well-known murexid reaction, like pure uric acid or other urates. (Plate II., fig. 5.)

4. *Acid Urate of Calcium* occurs only rarely and in small quantity. It forms a white amorphous powder, difficultly soluble in water, and on ignition leaves a residue of carbonate of calcium.

A specimen of the acid urine, in which the more or less colored amorphous sediment is suspended, is moderately warmed in a test tube. If complete solution takes place only urates are present, and the microscope with a two hundred to three hundred magnifying power will show the forms represented in Plate II., figs. 1 and 2. If a crystalline residue remains behind after heating, it may consist of uric acid with which a few crystals of calcic oxalate are frequently mingled. (Plate II., fig. 4.) In order to test more particularly for any bases present, the sediment is filtered off, washed with dilute alcohol, then dissolved in hot water, treated with hydrochloric acid, the uric acid which separates after twelve hours filtered off, the filtrate evaporated to dryness on the water bath, and the residue tested for potassium, sodium, calcium, magnesium, and ammonium, according to the common methods.

If the urine has an alkaline reaction, the uric acid in the sediment is present mostly as urate of ammonium, which can be readily recognized under the microscope from its sea-urchin-like spheres. (Plate II., fig. 5.) All the urates, like pure uric acid, give the well-known murexid reaction with nitric acid and ammonia. (§ 6, D, 8.)

The distinction of urate of sodium and potassium from the urate of ammonium under the microscope is easy, if the washed sediment is treated with hydrochloric acid and allowed to evaporate slowly on an object glass. The microscopic examination shows now in addition to the crystals of uric acid, cubes of chloride of sodium and chloride of potassium when the urates of sodium and potassium are present, and the leafy crystals of chloride of ammonium when urate of ammonium is present.

#### § 45. OXALATE OF CALCIUM.

A. *Presence.* Though oxalic acid is very widely distributed throughout the vegetable kingdom, it occurs only in very slight

amount in the animal organism, and then always in combination with calcium. In the urine calcic oxalate occurs both normally and pathologically as a sediment in the form of conspicuous crystals, especially in cases of disturbed respiration, emphysema of the lungs, rachitis, after epileptic convulsions, and during convalescence from severe diseases, especially typhoid fever. Calcic oxalate, however, occurs in solution also in urine which does not deposit a sediment, and may remain in solution a long time, since, besides other constituents of the urine, the acid phosphate of sodium especially possesses the power of dissolving calcic oxalate.

Calcic oxalate frequently accompanies the sediments of uric acid and urates. (Plate I, fig. 3 ; Plate II, fig. 4.)

Vegetable food, sparkling wines and beers, also the internal use of alkaline bicarbonates and salts with the organic acids, and of free uric acid and urates, often increase the amount of calcic oxalate in the urine.

The statements of Schunk,\* according to whom the oxalic acid of the urine takes its origin from the decomposition of the oxalurate of ammonium which is never wanting in normal urine, were not verified by me. In progressing decomposition of the urine oxalurate of ammonium is not, as Schunk believes, decomposed into oxalic acid and urea, but is transformed directly into carbonate of ammonium.†

B. *Microscopic Properties.* Oxalate of calcium, artificially prepared by precipitating a calcium salt with oxalate of ammonium, etc., appears under the microscope in perfectly amorphous masses, in which no trace of crystallization can be perceived. If it separates from the urine as a sediment, however, it shows very characteristic forms which are readily recognizable. The crystals of calcic oxalate appear in the form of small, elegant, shining, perfectly transparent, sharp-edged quadrilateral octahedra, which are highly refractive, and have a great resemblance to envelopes, but with these there are also sometimes a few very pointed ones. Beneke describes also peculiar hour-glass shaped crystals, and others which appear like quadrilateral prisms with pyramidal ends. (Plate I, fig. 3.)

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\* Proceedings of the Royal Society, vol. 16, p. 140.

† Zeitschrift f. analyt. Chemie, Band 7, p. 280.



Very beautiful calcic oxalate crystals can be easily separated from a urine which does not deposit a sediment, if it is covered with a layer of a dilute solution of oxalate of ammonium without stirring: I have artificially prepared in this manner a large number of the most beautiful forms. The behavior of calcic oxalate toward acid phosphate of sodium is interesting. If a solution of ordinary phosphate of sodium is treated with officinal phosphoric acid, until a drop of the mixture is no longer rendered turbid by a solution of chloride of barium, a proof that the fluid still contains only acid phosphate of sodium, dilute solutions of chloride of calcium and oxalate of ammonium can be added drop by drop without producing any cloudiness and separation of calcic oxalate. If then very dilute sodic hydrate is carefully added, drop by drop, to this mixture, which even after long standing remains perfectly clear, the calcic oxalate in solution separates after a time in very beautiful regular crystals. The acid solution, which is obtained by boiling uric acid with phosphate of sodium, can also hold calcic oxalate in solution, and after evaporation yields in addition to urate of sodium often very beautiful quadrilateral octahedra of calcic oxalate.

The crystals are insoluble in water and are scarcely affected by acetic and oxalic acids, but are readily dissolved by the strong mineral acids.

*C. Detection.* Since oxalic acid in the urine always occurs only in combination with calcium, it can very readily be recognized in all cases by its characteristic crystalline forms. The peculiar envelope form is especially important, since it renders confusion with other sediments impossible. The only possibility, perhaps, would be in confounding it with chloride of sodium, yet aside from the fact that the latter never occurs as a sediment, it is also sufficiently distinguishable from calcic oxalate by its solubility in water. Moreover, at times larger forms of calcic oxalate occur which have some resemblance to the crystals of ammonio-magnesian phosphate to be described presently, but the solubility of this double salt in acetic acid, in which, as we know, calcic oxalate is insoluble, as well as an accurate microscopic examination, does not allow of a mistake.

If, moreover, the urine is very acid, the crystals of calcic oxalate separate more readily if the free acid is nearly saturated and the urine is allowed to stand at rest for a time; for we



mentioned above that the crystals were quite soluble in a solution of acid phosphate of sodium. For this purpose the urine is placed in a small conical glass, and when the sediment has collected in the point, the supernatant fluid is poured off and a drop containing the sediment is put on a glass slide.

Calcic oxalate in solution may be detected with absolute certainty in the following manner: The urine to be tested (400 to 600 cc.) is treated with a solution of chloride of calcium, supersaturated with ammonia, and the precipitate which occurs dissolved in acetic acid, of which an excess is to be carefully avoided. After twenty-four hours the precipitate, in which uric acid is rarely absent, is collected on a small filter, washed with water, and a few drops of hydrochloric acid poured over it. Any calcic oxalate present is dissolved and the uric acid remains behind on the filter. The filtrate is diluted in a test tube with 15 cc. of water, and by means of a pipette is very carefully just covered with a sufficient amount of very dilute ammonia. The fluids gradually mix if left at rest, and after twenty-four hours all of the calcic oxalate present will have collected on the bottom, and under the microscope will appear in the form of the most beautiful octahedra.

I have frequently been able to prove the presence of tolerable amounts of calcic oxalate in solution in the urine by using this method, when no trace of it was to be discovered in the sediment; but I have also quite frequently tested normal urine for calcic oxalate with a negative result, so that I am still doubtful whether oxalic acid is to be reckoned among the normal or abnormal constituents of human urine.

#### § 46. EARTHY PHOSPHATES.

These sediments consist of calcic phosphate and ammonio-magnesian phosphate. It is very rare that only one of these compounds is met with; in most cases the two occur at the same time. On account of their ready solubility in very dilute acids, they cannot form in a strongly acid urine, but appear always only when the urine is but very feebly acid, neutral, or alkaline, so that the alkaline fermentation has already commenced either in the bladder or outside of it.

1. *Ammonio-Magnesian Phosphate*,  $\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$  [ $2\text{MgO}, \text{NH}_4$

$O, PO_4 + 12H_2O$ ]. This sediment is not met with in normal urine, but always appears in very beautiful crystals when the urine becomes very feebly acid or alkaline. In some diseases, in severe affections of the bladder and spinal cord, often the whole sediment consists of these crystals. Lehmann found a shining white sediment in a diabetic urine, which consisted only of the ammonio-magnesian phosphate without any traces of calcium.

The crystals of this double compound (triple phosphate) are always very easy to recognize from their conspicuous forms. The forms which occur most frequently are combinations of the rhombic vertical prism, which have a great resemblance to the lid of a coffin. (Plate II., fig. 3, fig. 5.) The crystals are insoluble in hot water, but acetic acid readily causes them to disappear, by which they are distinguished from similar forms of calcic oxalate. They are not attacked by alkalies.

2. *Phosphate of Calcium*,  $Ca_3(PO_4)_2$  [ $3CaO, PO_5$ ] and  $CaHPO_4$  [ $2CaO, H_2O, PO_5$ ]. This is an amorphous, and frequently also a crystalline powder. Phosphate of calcium is insoluble in water though soluble in acids, even acetic acid, and is precipitated from these solutions in an amorphous form by alkalies. It occurs also only in feebly acid, neutral, or alkaline urine.

Frequently, especially in urine with a feebly acid reaction, the phosphate of calcium is only held in solution by carbonic acid, and immediately separates in white flakes, very like a coagulum of albumen, as soon as the carbonic acid is driven off by heat.

Not very rarely also sediments of crystallized phosphate of calcium are found which frequently occur alone, but at times mixed with triple phosphate. The size, form, and grouping of the crystals of phosphate of calcium in the sediment varies very considerably, yet they always present sufficiently marked peculiarities to be immediately recognized under the microscope. The crystals are sometimes isolated, sometimes collected together; the latter is more frequent, in which case they form clumps and rosettes. Sometimes they are thin and needle-shaped, and then often form spherical rosettes of crystals by crossing each other at right angles and lying together; at times they are narrow and smooth and have sharp-pointed ends. But very frequently the crystals are thick, and more or less wedge-shaped, and are joined together by their pointed ends, so that

they describe more or less complete parts of a circle. The broad free end is usually somewhat oblique, and the more perfect crystals appear to be formed of six surfaces. Urine which separates crystallized phosphate of calcium in large amount is usually pale, considerable in quantity, and has a feebly acid reaction, but readily becomes alkaline in consequence of an admixture of mucus. Bence Jones says that this sediment may be produced at pleasure by taking lime-water or acetate of calcium. According to him, the crystallized phosphate of calcium is  $\text{CaHPO}_4$ ,  $[\text{2CaO}, \text{H}_2\text{O}, \text{PO}_4]$ , while the amorphous is  $\text{Ca}_2$ ,  $2(\text{PO}_4)$ ,  $[\text{3CaO}, \text{PO}_4]$ .

The two conditions on which the appearance of crystallized phosphate of calcium depends, but which need not exist together, are an excess of phosphate of calcium and a feebly acid reaction of the urine. If, therefore, normal urine is treated with a little chloride of calcium and nearly neutralized with sodic hydrate, it is often possible to obtain numerous crystals perfectly similar to those described.

*Detection.* The recognition of the earthy phosphates presents no difficulties, especially the first-mentioned, since its presence, as well as its microscopic and chemical properties, characterize it sufficiently. If they should occur mixed with other sediments, the following points will serve as distinguishing characteristics: Urates dissolve readily on heating the urine, phosphates remain undissolved even at a boiling temperature. Calcic oxalate, which in some forms may well be confounded with the ammonio-magnesian phosphate, is insoluble in acetic acid, whereas the latter is readily taken up. Free uric acid probably never occurs with the earthy phosphates, yet uric acid is readily recognizable both by its crystalline form and its solubility in alkalies. The murexid reaction finally would remove all doubt.

The familiar reactions serve to detect calcium, magnesium, and phosphoric acid. A small portion of the acetic acid solution is tested for phosphoric acid with uranium solution. The calcium is precipitated from a second specimen by an excess of oxalate of ammonium, and the phosphate of magnesium is precipitated from the filtrate by ammonia.

## § 47. CYSTIN.

Formula : $C_3H_7NSO_3$ , [ $C_3H_7NS_2O_4$ ]	{	Carbon	29.75
		Hydrogen	5.78
		Nitrogen	11.57
		Sulphur	26.45
		Oxygen	26.45
			<hr/>
			100.00

*A. Presence.* Cystin was first discovered in a urinary calculus, but later it has been found that, besides in such concretions, cystin often occurs also dissolved in the urine and may be precipitated by acetic acid. It also occurs as a sediment mixed with urate of sodium. The occurrence of cystin as a calculus is rare, for of one hundred and twenty-nine obtained only two contained cystin. (Taylor.) Recently Cloëtta found cystin in the fluids of the kidney together with inosite and hypoxanthin. Scherer discovered it once in the liver recently. J. Dewar and A. Gamgee state that they found cystin in the sweat in a few cases.

Julius Müller\* describes a calculus containing cystin which was removed by operation from the bladder of a boy six and a half years old. This boy's urine, obtained before the operation only in small amount, was alkaline, and deposited a sediment which was free from uric acid and earthy phosphates, and abounded in mucous corpuscles; there was only a little urate of sodium in solution, but much chloride of sodium. The calculus weighed  $268\frac{3}{4}$  grains and contained 55.55 per cent. of cystin. Directly after the operation the urine had an acid reaction, a mucous sediment, and contained less uric acid and earthy phosphates than normal urine. Eight weeks later, however, the alkaline reaction recurred again, and it contained much chloride of sodium and urea, but only traces of uric acid. On quiet standing it deposited a sediment of ammonio-magnesian phosphate and cystin; which, after removing the magnesium salt with acetic acid, was easily recognizable under the microscope by its crystalline form. The filtered urine also gave within

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\* Archiv d. Pharm., März, 1852, p. 228.

twenty-four hours after the addition of acetic acid a precipitate soluble in ammonia, on the evaporation of which most excellent microscopic tables of cystin were obtained. From this it follows that the production of cystin in the organism of the boy continued also after the operation.

Toel\* made interesting observations upon the formation of cystin on two girls in Bremen, by whom this remarkable body was constantly passed with the urine, as the result of a kidney trouble (nephritis calculosa), partly in solution, and partly as a sediment. The amount of cystin secreted amounted on the average to 1.4 gm. in twenty-four hours in each. Another very interesting case, in which cystinuria lasted for years, is described by Bartels.†

Not infrequently large concretions of almost chemically pure cystin are passed with urines containing cystin as a sediment. The little stones of yellow color and crystalline structure vary from the size of the head of a pin to that of a pea, and are so characteristic even in their exterior that they cannot readily be confounded with any other urinary concretion. Whoever has once seen them will always recognize them again at the first glance.

B. *Microscopic Properties.* Cystin crystallizes under the microscope in colorless, transparent, six-sided plates or prisms. Since, however, uric acid at times crystallizes also in six-sided tables, we must not rely on microscopic examination alone, but must carefully examine such a sediment chemically also. (Plate III., fig. 4.)

C. *Chemical Properties.*—1. Cystin is neutral without odor or taste, insoluble in water, yet soluble in mineral acids and oxalic acid, with which it forms saline, easily decomposable compounds. Acetic and tartaric acids do not dissolve it.

2. If cystin is heated with nitric acid, it dissolves with decomposition, and on evaporation leaves a reddish-brown mass which does not give the murexid reaction with ammonia.

3. Cystin does not fuse on being heated on platinum foil, but it inflames and burns with a bluish-green flame, while a sharp, acid, characteristic odor, like that of hydrocyanic acid,

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\* Annal. d. Chem. u. Pharm., Band 96, p. 24 *et seq.*

† Virchow's Archiv, Band 26, p. 419.

is evolved. On dry distillation it yields ammonia and a stinking oil, leaving a residue of porous charcoal.

4. Alkaline hydrates and carbonates, as well as ammonia, dissolve cystin with ease, but carbonate of ammonium does not. It is, therefore, always precipitated from its acid solution by carbonate of ammonium, and from its alkaline solution by acetic acid.

5. If cystin is boiled with potassic hydrate in which oxide of lead has been previously dissolved, a large amount of lead sulphide separates. (Liebig.)

6. If cystin is boiled with alkaline hydrates, ammonia and a gas which burns with a blue flame are evolved.

7. If a little cystin with a few drops of sodic hydrate are heated to boiling on a silver foil, there results a brown or black spot of sulphide of silver which cannot be washed away.

8. If cystin is dissolved by heating with potassic hydrate, diluted and treated with a solution of nitroprussiate of potassium, the well-known, beautiful, violet sulphur reaction occurs with great magnificence. (J. Müller.) This reaction is particularly beautiful.

*D. Detection.* Cystin is characterized especially by its crystalline form, its solubility in the mineral acids and alkalies, and by its behavior with nitric acid and with heat. Liebig has given besides for its recognition the reaction with caustic potash and lead oxide, which produce when boiled with cystin a very abundant precipitate of sulphide of lead. But in employing this reaction we must bear in mind that other bodies containing sulphur, such as albumen, fibrine, etc., exhibit a like behavior, so that we must first be convinced of the absence of these substances, and remove them if present.

Cystin is easily separated from the earthy phosphates and the urates by boiling and treating with acetic acid, since it is soluble neither in boiling water nor in acetic acid, while the latter are readily dissolved thereby. Uric acid which, as has been mentioned, at times also crystallizes in six-sided tables, is sufficiently characterized by its murexid reaction, since cystin treated in the same way leaves only a reddish-brown residue.

## § 48. TYROSIN.

(COMPARE § 37.)

Städeler and Frerichs observed in the urine of a woman suffering from acute atrophy of the liver, after standing awhile, a sediment of greenish-yellow spherical crystals, which considerably increased after slight evaporation of the urine. It was extracted with dilute ammonia, and the first crystals which formed from the solution were recognized as tyrosin. Another more soluble body, probably homologous with tyrosin, whose quantity of nitrogen amounted, not as in tyrosin to 7.73 per cent., but to 8.83 per cent., remained in the mother liquor.

O. Schultzen and L. Riess\* found the same sediment in acute atrophy of the liver. The clear urine, removed from the bladder with the catheter, on cooling deposited delicate almost colorless needles aggregated into sheaf-like bundles, which were recognized by all of the reactions as tyrosin.

## § 49. XANTHIN (HYPOXANTHIN?).

(COMPARE § 5.)

Bence Jones† found in the urine of a boy nine and a half years old, who three years before had had the symptoms of renal colic, whetstone-shaped microscopic crystals (fig. 3, a),

FIG. 3.



which, as the figure shows, might at first sight be considered as uric acid, but on heating the cloudy urine the sediment quickly dissolved. This sediment collected on a filter and washed with alcohol gave the following reactions: The crystals were soluble in water and hydrochloric acid, solution took place in nitric acid without effervescence, and after evaporation a yellow residue remained.

The hydrochloric acid solution on evaporation separated crystals of the form b, which were soluble in water. The sediment also readily dissolved in alkalies.

\* Loc. cit., p. 70.

† Chem. Centralblatt, 1868, p. 847.

The urine always had a tolerably high specific gravity, and at times contained traces of albumen, but the sediment, according to Bence Jones consisting of xanthin, did not appear again later.

G. Lebon\* describes an interesting calculus containing xanthin. It consisted first of all of a layer of phosphate of calcium and ammonio-magnesian phosphate one millimeter thick, then followed a second layer of calcic oxalate of equal thickness, and finally the chief mass consisting of xanthin and a small amount of urate of calcium. This inner stratum formed an amorphous cinnamon-brown mass which assumed a waxy lustre on being rubbed. The solution in hydrochloric acid on slow evaporation left a residue of beautiful hexagonal lamellæ of chloride of xanthin.

## II. ORGANIZED SEDIMENTS.

### § 50. MUCUS AND EPITHELIUM.

It is well known that animal mucus is separated from the mucous membranes and contains the epithelial cells in their different forms suspended in it. Every urine contains such mucus which comes from the urinary passages and bladder, and very soon separates when at rest as a light cloud. If such urine is filtered, the mucus for the most part remains on the filter in isolated transparent colorless clumps, which shrink and form a shining varnish-like coating.

The characteristic constituent of mucus is mucin, a derivative of the protein bodies, which when dissolved in a fluid, even in small amount, imparts to it a viscid stringy quality. A solution of mucin does not coagulate on boiling (distinction from albumen), but it does on the addition of alcohol, by which the mucus is precipitated as a fibrinous coagulum. Acetic acid and a solution of alum separate mucus in thick flakes; the stringy mass precipitated by acetic acid has a certain resemblance to coagulated blood fibrine. (Funke, Taf. XI, fig. 6; 2<sup>e</sup> Aufl., Taf. XV., fig. 6.) Mineral acids also precipitate a solution of mucin; yet the precipitates which take place are readily soluble in a slight excess of the acid. Mucin is chiefly distinguished from

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\* Compt. rend., Band 78, p. 47.



pyin, which occurs in pus, in that it is not precipitated either by a solution of corrosive sublimate or one of sugar of lead, though it is by the basic acetate of lead.

In the mucous sediment of a normal urine there appear under the microscope, besides the distinctly nucleated, variously shaped epithelial cells of the urinary passages, etc., isolated mucous corpuscles in the form of round, very granular cells, containing one or several nuclei, which do not differ from the colorless corpuscles of the blood, lymph, chyle, and pus in any essential particular. (Plate I., fig. 4, 5, and 6; Plate II., fig. 1, 2, and 3; Plate III., fig. 3.)

If the secretion of mucus is increased by disease, the little cloud described above as occurring in normal urine is often enormously augmented, and shows large amounts of mostly well-preserved epithelial flakes and mucous clumps. If the mucous sediment which settles on standing is free from pus and consists only of mucus, the filtered urine is free from albumen, while if pus is present at the same time the urine always contains an amount of albumen corresponding to the pus serum. (Compare Pus, § 52, B.)

In gonorrhœas the mucous corpuscles coming from the urethra differ from uric acid, etc., by their size and their clear, slightly granular appearance. In affections of the prostate the amylaceous bodies of this gland appear, and frequently, as at times after gonorrhœa, long mucous plugs, which under the microscope appear to be composed of mucous corpuscles closely adherent to each other.

1. Normal urine always contains only traces of mucin in solution. An increase, according to Reissner,\* occurs in various acute febrile affections, as pneumonia, pleuritis, typhoid fever, intermittent fever, pulmonary and intestinal catarrhs, meningitis, acute delirium, and epileptic attacks with irritation of the vascular system, etc. Often the mucin alone appeared at the commencement of the fever, a few days later albumen was also found, which disappeared again after a longer or shorter time, while the mucin continued a few days longer. Cases in which there was a large amount of mucin which lasted a long time without albumen were rare. The microscope showed for the most part a large number of epithelial cells of very different

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\* Archiv f. path. Anat., Band 24, p. 191.

sorts ; mucous coagula were often very abundant, but at times were only sparingly present. Sometimes mucous and pus cells were entirely wanting. Acetic acid is especially valuable for the detection of dissolved mucin ; it causes in every urine containing mucin a uniform cloudiness insoluble in an excess of the acid. Only in rare cases does a flocculent deposit occur after long standing, but if the urine before the addition of acetic acid was diluted with water to several times its volume, there results from the cloudiness, when there is not too small an amount of mucin, a tolerably coarse flocculent precipitate which settles after some hours' standing, and under the microscope appears as a uniform finely granular mass with a few uric acid crystals imbedded in it. Tartaric acid acts like acetic acid. Mineral acids when very dilute, and added drop by drop to the urine, give a precipitate which is soluble in the slightest excess of acid. A few drops of hydrochloric acid will also dissolve the cloudiness caused by acetic acid immediately and completely, when added soon after the latter.

Many urines in very febrile conditions also give a cloudiness with acetic acid insoluble in an excess, but which disappears on heating and does not recur again, if the urine is sufficiently diluted with water before the addition of the acid. This cloudiness, which is probably caused by urates, is, therefore, easy to distinguish from a precipitation of mucin.

The dissolved mucus is frequently precipitated in the form of mucous coagula at the beginning of acid fermentation, probably by the free acids formed. They appear in narrow and broad curved bands containing very fine points and granules arranged in rows, and very frequently sediments of acid urates accompany them. These mucous coagula (Plate II., fig. 2) have at times a certain resemblance to granular casts from the kidney (Plate I., fig. 6), and may, therefore, give rise to mistakes. With a little experience, however, they are both easily distinguished.

2. Epithelial cells are found in three different forms :

a. Round cells from the urinary tubules of the kidney, and from the deeper layers of the mucous membrane of the pelvis of the kidney. They are for the most part swollen by the salts contained in the urine, and appear as complete spheres with distinctly formed nuclei.

The epithelium of the male urethra is very similar to renal epithelium, so that the two can scarcely be distinguished by the microscope. When renal epithelium is present, the urine usually contains albumen at the same time.

b. Conical and tailed cells in most cases have their origin from the pelvis of the kidney. These cells are usually twice as long as they are broad, and are broader at one end than at the other. The spindle-shaped prolongation occurs either at one end or at both.

c. The flat cells come either from the vagina or bladder. In most cases they form irregular polygonal lamellæ with distinct nuclei situated nearly in the centre.

### § 51. BLOOD.

The occurrence of blood in the urine is not a very rare appearance and its recognition presents no special difficulties. For our purpose the blood corpuscles, and especially their microscopic properties, are of special importance.

A. *Microscopic Properties.* Normal blood corpuscles are small, round, solid structures, which seen under the microscope present a shape not to be confounded with any other substance; they appear as thick, circular, slightly biconcave, yellow disks, with rounded edges. Their size in human beings amounts to about 0.00752 mm. (Plate I., fig. 6; Plate III., fig. 1 and 2.) The normal forms, however, suffer peculiar modifications and changes due to the presence of many alkaline salts and other substances. These changes are of special importance for our purpose.

1. *Action of Water on Blood Corpuscles.* According to the amount of water added and the time during which it acts, the blood corpuscles undergo various changes, which are figured in Plate III., fig. 2, proceeding from left to right. The first result of the action of water is, that the single cells swell up, at the same time assume a more lenticular shape, and finally become spherical; this takes place because their central depression disappears and gradually arches out, which necessarily causes a diminution of the diameter of the disks. The corpuscles now appear smaller, the central shadow disappears gradually, and in its place a circular one appears on the edge.

If the action of the water lasts for a long time, the cells become constantly fainter and paler, and finally appear only as hyaline bladders, which soon become entirely imperceptible and disappear.

2. *Action of Saline Solutions on Blood Corpuscles.* If normal blood corpuscles are covered with a concentrated solution of a neutral salt, for example sodic sulphate, they undergo quite rapidly a strong contraction, which under the microscope is chiefly indicated by an increase of the central depression; the shadow which indicates this reaches nearer to the edge of the disk than in normal blood corpuscles. The edges are usually no longer circular, but are mostly more or less distorted, oblong, angular, and also not smooth, but notched or toothed. If, further, blood corpuscles, which have become invisible by the action of water, are treated with a concentrated solution of sulphate of sodium, they become visible again, but now appear in the distorted, angular, and toothed forms just described. (Plate III., fig. 2, lower right side.)

3. Caustic alkalies, as well as several organic acids, as, for example, acetic acid, cause the blood corpuscles to become very much swollen and distorted, and destroy them more or less rapidly.

The important constituent of the red blood corpuscles is the hæmoglobin (blood-coloring matter, hæmatocrystallin), which may be obtained more or less easily in a crystalline form. (Funke, Taf. X., fig. 1-6; 2<sup>te</sup> Aufl., Taf. IX. u. X.) The beautiful blood-red solution shows on great dilution ( $\frac{1}{1000}$ ), when it is examined by the spectroscope in a layer of fluid one ctm. thick, two absorption bands between the Fraunhofer lines D and E in the yellow and green of the spectrum. (Plate IV.) The band situated nearer D is more sharply defined, and also disappears later than the other on dilution. If, however, such a solution of oxyhæmoglobin is allowed to remain in a closed vessel for a time, or if the oxygen is removed from it by a few drops of sulphide of ammonium, the arterial color gradually disappears. In the spectrum the two absorption bands are now absent, and instead, about in the middle between the spectral lines D and E, there is a broad, poorly defined band. On shaking with air this disappears, and the absorption bands characteristic of oxyhæmoglobin appear again. If a solution of

hæmoglobin is heated a few minutes to 70° or 80° C., it decomposes into hæmatin and coagulated albumen with change of color. Basic acetate of lead does not precipitate a solution of pure hæmoglobin. After standing a long time, especially at blood heat, a darker color and acid reaction occur, the hæmoglobin becomes converted into methæmoglobin, which is an intermediate product formed during the change of hæmoglobin into hæmatin and albuminoid matter, and which is found in old extravasations of blood and also in the urine after destruction of the blood corpuscles. Examined with the spectroscope an acid solution of methæmoglobin sufficiently dilute shows almost the same spectrum as an acid solution of pure hæmatin. Both give only one absorption band between the lines C and D, which lies rather nearer C. (Plate IV.) If the solution is rendered alkaline the bands draw nearer to D, and become feebler and less sharply defined. Basic acetate of lead precipitates a solution of methæmoglobin. We are indebted to Hoppe-Seyler and Stokes for these excellent reactions.

*B. Detection.*

1. *The Urine contains Blood Corpuscles.* If the urine is acid, the blood corpuscles remain unimpaired a tolerably long time, or at most become somewhat crenated, but they are usually swollen and approach the spherical form. Their color is paler than in the normal condition, but they are always at the same time sharply defined, and are no longer arranged in rows. All of these changes indeed are to be attributed to the water and salts contained in the urine according to the modifications described above. (Plate I., fig. 6; Plate III., fig. 1 and 2.) When the amount of blood is small, the urine is allowed to stand quietly in a conical glass for a long time. The blood corpuscles then settle to the bottom as a beautiful red sediment, and may generally be recognized as blood with the unaided eye. The clear filtered urine, when blood is present, always contains a corresponding amount of albumen also, which may be recognized according to § 23, D.

If such a urine sufficiently diluted is examined with the spectroscope, it shows the absorption bands between the lines D and E, which were described above as characteristic of hæmoglobin. (Manipulation: see below, 2, a.) (Plate IV.)

2. *The Blood Corpuscles are destroyed; the Urine contains Me-*

*thæmoglobin.* The urine may be colored reddish brown, or even black, by methæmoglobin. It is tested as follows:

a. Some of the clear filtered urine is poured into a vessel, *a*, fig. 4, of plate glass, with two parallel walls; this is placed close to the slit of the spectroscope, lighted with sunlight or a bright gas or oil lamp, and the spectrum observed through the telescope, *b*. If the amount of methæmoglobin is not too great, and the urine consequently not too strongly tinged, the characteristic bands between the lines C and D will appear imme-

FIG. 4.

diately somewhat nearer C than D. (Plate IV.) On the other hand, when there is very considerable methæmoglobin, a greater or less part of the whole spectrum will be absorbed and will only become clear on diluting the urine under examination with water, until the absorption bands characteristic of methæmoglobin are seen.

b. A second specimen of the filtered urine is heated to boiling. If methæmoglobin is present, a brownish-red coagulum is formed, which consists of hæmatin and an albuminoid body: after drying the color becomes almost black. If we treat such

a coagulum, previously washed, with alcohol containing sulphuric acid, and heat gently, it will assume a more or less red or reddish-brown color, and after sufficient concentration will show in the spectrum the absorption bands described under a, as characteristic of hæmatin and methæmoglobin. (Plate IV.)

c. A third specimen of the urine under examination is treated with a little sodic hydrate, heated to boiling and allowed to stand for a time. The earthy phosphates which separate carry down the hæmatin formed by the decomposition of the hæmoglobin or methæmoglobin, and appear sometimes as a brownish-red and sometimes as a beautiful blood-red precipitate, which is often dichroitic, playing into green by reflected light. This reaction does not allow of a discrimination between hæmoglobin, methæmoglobin, and hæmatin.

If the phosphate precipitate is colored by rhubarb, senna, or santonin, and not by hæmatin, it is recognized by the fact that it does not, like the hæmatin precipitate, become dichroitic by the action of potassic hydrate, but in time becomes violet, especially when exposed to the air.

d. Tannin is a very valuable reagent for precipitating small traces of blood. The fluid in question is treated with a little ammoniac or sodic hydrate, then with a solution of tannin, and lastly with acetic acid until it has a distinctly acid reaction. If blood is present a distinctly colored precipitate forms, which quickly settles to the bottom of the fluid. This precipitate is tannate of hæmatin. After washing and drying, it is specially fitted for the production of hæmin crystals. For this purpose a portion of the dry precipitate is placed on a glass slide, a trace of chloride of sodium is added, and then glacial acetic acid. Solution takes place at a gentle heat, and after cooling, the well-known characteristic hæmin crystals will be found under the microscope in large numbers. (Struve.)\* The reaction is extremely delicate. By performing it in the manner described, Berg† succeeded in proving by the most beautiful hæmin crystals, the presence of a drop of blood in 450 cc. of urine.

e. Another method for detecting blood in the urine has been given by Almén.‡ A few cc. of tincture of guaiacum are mixed

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\* Zeitschrift f. analyt. Chemie, Band 11, p. 29.

† Hyica, Band 34, 2, Stockholm, 1873.

‡ Zeitschrift f. analyt. Chem., Band 18, p. 104.



with an equal volume of oil of turpentine, it is shaken till an emulsion is formed, and then the urine to be tested is carefully added. When the emulsion comes in contact with the urine, the guiac resin is quickly precipitated as a white, later dirty yellow or green precipitate. If the urine contains blood, even traces merely, the resin is colored more or less intensely blue, often almost indigo blue. In normal urine or in urine containing albumen from pus, this blue coloration does not occur.

## § 52. Pus.

When urine contains pus it can only be detected with certainty by the microscope.

A. *Microscopic Properties.* Normal pus corpuscles appear under the microscope as round, pale, faintly granular bodies of variable size. It is of especial importance that a distinct nucleus may usually be perceived in them, which in many corpuscles is single, but in others appears divided and multiple. (Plate I., fig. 6; Plate III., fig. 3.) All pus corpuscles do not have a sharp contour, but in many cases only a faint and indistinct one.

1. *Action of Water on Pus Corpuscles.* If fresh pus is considerably diluted with distilled water, the corpuscles are seen to swell up very much, and become extremely pale and delicately bordered; at the same time their granular surface usually disappears, whereas the nuclei become more distinct and small dark punctiform granules are seen. (Funke, Taf. XI., fig. 4; 2<sup>a</sup> Aufl., Taf. XV., fig. 4.)

2. *Action of Acetic Acid on Pus Corpuscles.* If dilute acetic or any other organic acid, or even very dilute mineral acids are allowed to act on pus, the corpuscles swell up, so that sometimes they assume double their usual size; their surface then loses its granular appearance, the coverings become very hyaline, and not unfrequently burst, so that here and there, with a good light, their jagged and broken remnants may be distinguished. The nuclei already mentioned become very distinct, of different shapes and numbers, appearing partly as simple, round, oblong, spindle and horseshoe-shaped bodies, and partly as double, triple, and quadruple ones, variously grouped accord-



ing as they are formed by division of the single nucleus. (Plate III., fig. 3, upper half.)

3. *Caustic Alkalies* quickly destroy pus corpuscles, but complete solution does not take place. The corpuscles frequently remain visible for a short time, but disappear after the addition of water, and leave only a gelatinous residue in which isolated bright or dark points may be recognized.

B. *Detection.* Pus settles very quickly in acid urine when at rest, and when the supernatant urine has been drawn off with a siphon, it may be easily subjected to microscopic examination. (Plate I., fig. 6; Plate II., fig. 3; Plate III., fig. 3.) Purulent sediments are not very rarely accompanied by blood corpuscles, which may be recognized by their reddish color, but more surely by the microscope. In both cases the clear filtered urine contains corresponding amounts of albumen. (§ 23, C.) Pus suffers an essential change in alkaline urine, which is the more important, since frequently in catarrh of the bladder, etc., alkaline urine is passed with considerable amounts of pus. Alkalies change pus into a gelatinous mucous mass, which adheres tenaciously to the wall of the vessel, and under the microscope pus corpuscles no longer appear, so that it may readily be mistaken for mucus. But in most cases it is possible to find in addition to this viscid gelatinous mass a tolerable number of pus cells suspended in the urine if it is examined under the microscope as soon as possible after being passed. The behavior of pus with alkalies just cited may serve for distinguishing it from mucus. The sediment under examination, obtained by settling, is treated with concentrated potassic hydrate; pus is coagulated by it into the gelatinous mass spoken of, while mucus dissolves to a thin fluid with flakes. (Donné's pus test.)

Since, as observed above, when pus is present, the urine always contains albumen also from the pus serum, an approximate estimation of the quantity of pus may be made from the amount of the albumen in the urine previously filtered, provided there is sufficient ground for excluding a simultaneous real albuminuria. Moreover, when blood is present at the same time, this is also to be taken into account as the source of a part of the albumen.

## § 53. CASTS.

In many diseases, but especially in Bright's disease of the kidneys, peculiar tubular or cylindrical bodies, which have for a long time been the subject of investigation, are observed in the sediment of the urine. They vary in texture more or less, for which reason Lehmann distinguishes three different kinds :

1. Tubes which appear to consist of the epithelial lining of the tubules of Bellini ; these appear in almost every inflammatory irritation of the kidneys, and form regular tubes in which the small cells and cell nuclei appear to be grouped almost like a honeycomb. (Plate I., fig. 4.)

2. Cylinders which appear to consist of fresh exudation, which was formed in the tubes of Bellini and has retained their form. These cylinders form granular masses which are frequently covered with blood and pus corpuscles. They appear to consist of fibrine, at least their ready solubility in alkalies indicates this, while the blood and pus corpuscles attached are partly destroyed and partly remain suspended in the fluid. They are always found in Bright's disease.\* (Plate I., fig. 6.)

3. Finally, casts are sometimes observed, which consist of hollow cylinders with hyaline walls, and can be distinguished from the surrounding fluid under the microscope only with care. Frequently they lie together, form folds and appear as if twisted on their axis. They usually occur only isolated in the chronic form of Bright's disease. (Lehmann.) (Plate I., fig. 5.)

*Detection.* For the certain detection of these very important structures, the urine, which in most cases contains considerable albumen, is allowed to stand several hours in a conical glass. The collected sediment, mostly white and flaky, or, when other matters are present also, forming thick masses, is first examined with a power of one hundred and eighty or two hundred diameters, and if these structures are present they can readily be seen. At most the very hyaline cylinders mentioned under 3 may remain unobserved, but immediately become apparent when the object is colored yellow by the addition of a solution of iodine in iodide of potassium, or red by the addition

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\* Frerichs, Bright's disease.

of a not too concentrated solution of fuchsin. Since frequently only a small number of these casts occur, a number of preparations must be made and each one carefully examined in order to be sure of their absence. These sediments are frequently accompanied by fat drops, pus, epithelium, blood, etc.

Care is to be taken not to mistake for granular renal casts those mucous casts described in § 50, under mucus, which are frequently found in acid urine together with urates. (Plate II, fig. 2.) (Compare Mucus, § 50.)\*

Concerning cancerous and tuberculous masses, see in the second part.

#### § 54. SPERMATOOA.

Spermatozoa appear under the microscope as spherical or nearly spherical elements, with a distinctly recognizable tail, which is usually pointed. They appear to have a spontaneous movement. We find them in the urine after masturbation or coitus, but they have been not unfrequently observed in the urine of typhoid-fever patients.

It is very easy to find spermatozoa on account of their characteristic shape, which does not admit of their being confounded with anything else. At the same time spermatozoa are very indestructible, so that the diagnosis of semen in the urine is rendered still more easy. In order to find them it is necessary to place the urine at rest for a few hours at least in a conical glass (champagne glass), since the spermatozoa then sink to the bottom with the flakes of mucus. By carefully decanting, the greater part of the supernatant fluid is removed and a drop of the sediment in the apex of the glass is placed under the microscope. If spermatozoa are present they appear in the above-mentioned tadpole-shaped form. To detect them a magnifying power of from three to five hundred diameters is necessary. They soon lose their power of motion in pure water, and in urine also, especially when strongly acid or alkaline; the spermatozoa at the same time undergo a peculiar

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\* C. L. Rovidia, Ueber das Wesen der Harncylinder. Jahresbericht u. d. Fortschritte d. Thierchemie von R. Maly, 1872, p. 184 und 187.

H. Senator, Ueber die im Harn vorkommenden Eiweisskörper und die Bedingungen ihres Auftretens bei den verschiedenen Nierenkrankheiten, über Harncylinder und Fibrinausschwitzung. Virchow's Archiv, Band 60, p. 476.

change of shape: they form hooks (Oesen) by the posterior part of the organism being bent forward like a loop, or coiled around the forward part. Moreover, the observation of Lehmann is worthy of mention, viz., that urine containing semen very readily becomes alkaline, and shows in the mucous sediment, even when few spermatozoa are found, peculiar, fine, laminated, very transparent flakes.

Clemens has several times observed the passage of immature semen with the urine; this consists of those seminal cells, in which the spermatozoa still lie in the envelope with head and tail attached to it; these spermatozoa seldom showed any movement, such as is familiar in mature semen. Together with these sperm-cells Clemens often saw in the urine of patients suffering from spermatorrhœa spherical cells of 0.0033 to 0.005'' diameter filled with fine granules, which were mostly located on one side of the cell. These cells are nothing more than the mother cells of the spermatozoa. These elements are found chiefly in the last drops of urine passed by patients badly afflicted with spermatorrhœa, and also in those suffering from typhoid fever.\*

#### § 55. FUNGI. INFUSORIA.

Fungi and infusoria are observed under the microscope in all urine which has stood for a long time; they are found also in fresh urine which has already begun to decompose in the bladder, as is quite frequently the case in catarrh of the bladder.

The infusoria are usually very small. Most frequently punctiform monads or vibriones arranged like strings of pearls and often branched are found, and are especially abundant in urine containing mucus or albumen after standing awhile. According to the investigations of L. Daille,† living vibriones very frequently occur in pathological freshly passed urine, in which, according to the form, size, and sort of movement, six different varieties may be distinguished. The smallest of these vibriones are  $\frac{1}{1000}$ , the largest  $\frac{1}{60}$  mm. in size. They do not occur in the urine of all sick persons. Daille, however, claims to have

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\* Canstatt's Jahresbericht, 1860, p. 285.

† Journ. d. Pharm. et de Chim., 1865, II., 450; also Wittstein's Vierteljahresschrift, Band 16, p. 67.

found that the urine of patients affected with lung diseases constantly shows such infusoria either directly or a short time after passing. I must also remark, that according to Hallier,\* very different forms of fungus, such as vibriones and leptothrix-formations, have been frequently described as bacteriæ and monas crepusculum, especially by Pasteur. Hassall observed a second sort of infusoria occurring in the urine, the Bodo urinarius. The living moving individuals are oval or round,  $\frac{1}{1800}$ " long, and  $\frac{1}{3000}$ " broad, granular and similar to mucous cells. Some times they are broader at one end and furnished at different points with one, two, or three threads or ciliæ. They increase by division. Among those described, they have, according to Hassall, most resemblance to the Bodo intestinalis. (Ehrenb.) They are said to occur very frequently in albuminous urine together with vibriones.

Of spores, the urinary fermentation spore is very frequently found in the form of round or oval nucleated cells, which spring especially from the decomposed mucus. These fermentation spores lie at times isolated and at times aggregated together forming rows and groups. (Plate II., fig. 2 and 4.) In the advanced stage of fermentation they frequently accompany the sediments of urates, free uric acid, and calcic oxalate.

According to von Tieghem the alkaline fermentation of urine depends on the development of a Torulacea, which consists of spherical non-granular cells arranged in rows like a rosary, and showing no positively recognizable distinction between envelope and contents; they are 0.0015 mm. in diameter. This ferment appears to increase by budding, and never develops on the surface of the fluid, but either within it or on the bottom of the vessel, where it finally forms a white deposit mixed with the separated salts. According to Hallier† in the ammoniacal fermentation only the so-called nucleated cells are active, for when he sprinkled boiled healthy human urine with the spores of penicilium, there developed from the swarms only so-called nucleolar cells in incredible numbers.

The oval transparent yeast spores which form during the fermentation of diabetic urine, are considerably larger than the

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\* Hallier's Gährungserscheinungen, Leipzig, bei W. Engelmann, 1867, p. 5, 66, etc.

† Loc. cit., p. 64.

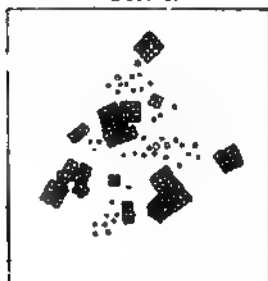
above, and in form and development correspond to the ordinary yeast cells. Their form is usually somewhat oblong, sometimes also round, their size is variable; all have a distinct round nucleus which often appears like a hole. According to Hallier spores also form in the bladder, especially leptothrix chains, from which the yeast fungus may form even within the bladder in diabetic urine. On the surface of old diabetic urine forked, branched, confervæ threads containing spores frequently form, which after the urine has stood a long time often make such a thick maze that they cover the entire field. (Fig. 5.) It is asserted by Hallier and others that these more highly organized fungi may under favorable conditions spring from the yeast cells, but this is positively denied by De Bary and Reess.\* Besides those mentioned, Hassall has found other forms of fungi in alkaline albuminous urine.

FIG. 5.

Finally, the discovery of Letzerich is worthy of notice† that more or less considerable masses of fungi, spores, and mycelium occur in the urine in diphtheritis. The mycelium was bedded in finely granular, somewhat yellow-colored masses of exudation, which floated in the urine and made it faintly cloudy.

*Urinary Sarcinæ* have been found again by Ph. Munk in the urine of a man forty-three years old. The freshly passed urine

FIG. 6.



had a constantly alkaline reaction, it was cloudy, and contained a little albumen. Under the microscope, in addition to the epithelium, a few blood and pus corpuscles, vibriones, and triple phosphate, and a large number of clear white cubes of sarcinæ, rounded a little on the corners, were found. (Fig. 6.) If the urine stood for a while, a very abundant whitish deposit soon formed,

which consisted chiefly of sarcinæ and the other bodies men-

\* M. Reess, "Die Alkoholgährungspilze," Leipzig, 1870, bei Arthur Felix.

† Virchow's Archiv, Band 52, p. 233.

tioned, and especially in the months of May and June occupied a fifteenth or a twentieth part of the whole height of the daily amount of urine when emptied into a glass. In the autumn months the sarcinæ decreased, and at the end of October were almost gone.

Munk found single sarcinæ elements and cubes formed of eight, sixty-four, and five hundred and twelve elements. Fragments of larger cubes were found, especially from those consisting of five hundred and twelve elements, in addition to the above forms. The single elements had a magnitude of 0·0008 to 0·0016 mm.; the cubes consisting of eight elements had a breadth of from 0·0016 to 0·0034 mm.; those consisting of sixty-four element, a diameter of 0·0032 to 0·006 mm.; while those consisting of five hundred and twelve elements had a diameter of from 0·008 to 0·012 mm. The sarcinæ from the urine were considerably smaller than the sarcinæ from the stomach. The only form of sarcinæ which can be indubitably recognized is that of the cube described by Virchow, which is especially well seen when the preparation is made to roll under the microscope. No tables or plates were to be seen. The reaction of the urine appears to have no influence on the development of sarcinæ; in this case it was constantly alkaline, in the one observed by Welker it was acid, in others occasionally neutral.\*

## V. ACCIDENTAL CONSTITUENTS.

### § 56.

This section embraces the changes which substances undergo on their passage into the urine. The importance of the study of these changes is at once apparent, since it gives us an insight into the complexity of the metamorphosis in the animal organism. Yet to obtain uniformly good results in this respect naturally a very great series of investigations are necessary, which must be accurately carried out even to the most minute detail, and indeed best by the assimilation of organic bodies whose chemical composition is perfectly known, and whose products of decomposition have been accurately investigated in all

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\* Archiv f. path. Anat. u. Physiol., Band 22, p. 570.



directions, because from the changes which such compounds suffer in the economy conclusions may be drawn concerning the chemical processes which are at work in the organism, and especially in the blood, in the metamorphosis of tissue.

Before passing to the individual substances the following facts are to be mentioned :

In general it is self-evident that only those substances can pass into the urine which, in the first place, do not serve as food, and secondly, are soluble in water and have no tendency to form insoluble compounds with the organic or inorganic constituents of the body. For these reasons, therefore, it is quite easy to find most of the soluble alkaline salts again unchanged in the urine. But if we introduce into the body a non-oxidized material which has a tendency to take up oxygen, we find it in the urine again oxidized ; such a body, for example, is sulphide of sodium, which always appears in the urine in the form of sulphate of sodium. But all substances which form insoluble or difficultly soluble compounds with the constituents of the body, as for example, most metals which unite with the protein matters as Orfila has found, only appear in the urine again when they have been supplied to the economy in very large amount.

Many organic bodies, moreover, suffer in the organism similar or the same changes which we are able to bring about artificially by the action of permanganate of potassium or ozone, in neutral or alkaline solution. Others again become so completely oxidized that it is not possible to detect either them or the products of their decomposition in the urine, while many give off oxygen and appear in the urine as lower stages of oxidation.

Lastly, the length of time is to be observed which is required for the elimination of a substance with the urine. It may be assumed as a rule, that readily soluble substances will be quickly removed again from the body with the urine, yet individuality appears to exercise some influence in this respect ; thus, Lehmann has observed that after a dose of ten grains of iodide of potassium no trace of iodine can be found in the urine in many persons twenty-four hours afterward, while in others it will be found often three days afterward.

We will now consider the behavior of different substances in the economy.



## I. INORGANIC SUBSTANCES.

A. *Salts of the Heavy Metals.*

Since the salts of the heavy metals form difficultly soluble compounds with many animal matters, especially the protein bodies, they only appear in the urine again when they have been taken into the economy in large doses. Orfila found antimony, arsenic, zinc, gold, silver, tin, lead, and bismuth in the urine after large doses, while they can at other times only be found in the liver and its secretions and the solid excrements, when they are given in relatively small and frequently repeated doses.

Iron, after its internal administration, can frequently be detected immediately in the fresh urine by the ordinary reagents. (Lehmann.)

Arsenic, according to Roussin, is said to exist in the urine as ammonio-magnesian arseniate. Lead was directly detected by Moos in the urine, by means of sulphuretted hydrogen, on the third day after a daily dose of from eight to nine grains.

To detect the heavy metals in the urine the same methods are to be followed which are adopted in legal cases to discover them in presence of organic matters. I therefore content myself with referring to Fresenius's guide to qualitative analysis.

*Mercury.* Recently, electrolysis has frequently been successfully employed to detect mercury in the urine, and on account of the importance of this subject the method made use of by Schneider for this purpose may be mentioned here. Five grams of chlorate of potassium are dissolved in one liter of the urine to be examined, hydrochloric acid is added until the reaction is strongly acid, and then it is heated on the water bath. If the color becomes dark during the evaporation, a fresh amount of the oxidizing medium is to be added, but the heat is to be continued until a specimen after the addition of hydrochloric acid has no bleaching action on coloring matters. On the contrary, it is no advantage to continue the evaporation of the urine until the salts crystallize out, since the fluid becomes colored dark when concentration is pushed to this point. Besides, such highly concentrated solutions are not well fitted for electrolysis, as Schneider has convinced himself by many experi-

ments. In most cases very large amounts of urine are necessary. Schneider took the entire quantity of urine passed during from three to six days (seven to fifteen liters) for his experiments. After the addition of chlorate of potassium and hydrochloric acid it was concentrated on the water bath to one-seventh or one-eighth of its volume. Schneider used for the electrolysis of the fluid thus prepared a Smee's battery of six elements (other constant chains are naturally quite as efficient), whose anode consisted of a platinum plate four centimeters broad, and whose cathode was a gold wire one millimeter thick, which terminated in a club-shaped thickened end two millimeters in diameter. For the purpose of confining the division of the mercury to the smallest surface possible the electrolysis was performed in a vessel whose breadth was greater than its height. The electrolysis was continued eighteen to twenty-four hours. The gold thread, which at the end of the experiment appears to be amalgamated when mercury is present, is tested as follows: It is put into a carefully cleaned glass tube which is drawn out to a capillary point at one end, and the tube is then closed at the other. The broad portion of the tube which contains the metal is heated to a red heat throughout its entire length. If a sublimate is deposited on the cool part of the tube after about five minutes, it is driven by heating into the capillary portion, and then the metal is once more heated in order to ascertain if a new sublimate appears. Now that part of the tube which contains the metal is melted from the capillary end, so that a short piece of the wide portion remains behind as a flask-like dilatation. After cooling the dilated end is opened by nipping off the capillary end, then a little iodine is introduced into it by means of a glass thread, and it is again closed by heat. The iodine vapor is thus driven into the capillary part of the tube which contains the mercury and disappears; in its place brown, red, or yellow rings appear, according to the amount of iodine introduced. If the brown rings are very carefully heated, the iodine evaporates from them, and red rings of mercuric iodide remain. The red as well as the yellow rings volatilize on being strongly heated, but immediately deposit again on the cold portions as a red sublimate, but which under certain circumstances may be yellow. The yellow rings consist of mercurous iodide; they occur when the amount of

iodine which was added was insufficient to form mercuric iodide; if another small crystal of iodine is put into the capillary end, and heated, the yellow rings readily become red. Under the microscope the red crystals appear as four-sided octahedra, which are often so placed with their surfaces toward each other that they produce feathery crystals resembling those of ammoniac chloride.

No mercury could be detected by electrolysis in three cases in which the urine abounded in iodide of potassium, and which after the addition of chlorate of potassium and hydrochloric acid was concentrated to one-tenth. After these urines, however, were treated with sulphuric acid, which contained nitrous acid and were evaporated on the water bath until the iodine was completely removed, the cathode on repeating the electrolysis showed distinct traces of amalgamation, and the subsequent heat tests showed the most distinct reaction for mercury. It appears advisable, therefore, in urine which contains iodides to first free it from its iodine. This is easily done by heating on the water bath and gradually adding sulphuric acid which is saturated with nitrous acid.

Mayençon and Bergeret\* use the following simple method to detect mercury, which, however, is not in every case certain: An iron nail is suspended in the urine which is to be examined by means of a platinum wire, then pure sulphuric acid is added until oxygen is slowly evolved. The mercury now forms a metallic deposit on the platinum wire. After about half an hour the wire is removed, washed, and then exposed to the vapors of chlorine to convert the mercury into corrosive sublimate. If the platinum wire is then gently drawn over a piece of filter paper which has been moistened with a one per cent. solution of iodide of potassium, a red streak of mercuric iodide is obtained, which dissolves in an excess of iodide of potassium.

Kletzinsky evaporates the urine which has been treated with chlorate of potassium and hydrochloric acid to dryness, and extracts the residue with ether to remove the corrosive sublimate. This procedure, according to Schneider, is very uncertain, since some mercuric chloride combined with the alkaline

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\* Chem. Centralblatt, 1878, p, 678. Zeitschr. f. analyt. Chem., Band 18, p. 108.

chlorides in the form of double chloride is retained in the residue. These compounds are nearly insoluble in ether, and therefore no sublimate can be dissolved out by ether from the evaporated residue of the urine when completely dried. On account of the importance of this subject I give here the results obtained by Schneider :

1. In the urine of syphilitic patients who had never been subjected to treatment by mercury, no mercury could be detected by electrolysis.

2. The same negative result was obtained on testing the urine of individuals who had pursued a mercurial treatment a long time before. The investigations were commenced on different persons, fourteen days, five months, and half a year after the mercurial treatment.

3. The urine constantly contains mercury during the internal use of mercurial preparations.

4. The experiments of Schneider are by no means favorable to the views now quite generally entertained of the action of iodide of potassium on metals which are retained within the organism. In three cases where iodide of potassium was given immediately after treatment by corrosive sublimate this remedy distinctly did not increase the separation of mercury with the urine.

5. In a case of hydrargyrosis which ended fatally the urine abounded in mercury, though only 1,400 cc. could be obtained for examination. Also the brain and especially the liver contained it.\*

*Thallium.* According to W. Marmé thallium is readily detected by electrolysis in the urine after the latter has been treated with chlorate of potassium and hydrochloric acid and afterward concentrated. The metal fixed in this way on a platinum wire and carefully cleansed with distilled water is brought directly into the flame of the spectral apparatus, but in this case the anode as well as the cathode is to be tested.†

*Cadmium* is detected also by electrolysis of the urine after being treated with chlorate of potassium and hydrochloric acid.‡

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\* Schneider, über das chemische und electrolytische Verhalten des Quecksilbers in thierischen Substanzen. Wien in Commission bei K. Gerold's Sohn, 1860.

† Zeitschrift f. analyt. Chem., Band 6, p. 508.

‡ Zeitschrift f. analyt. Chem., Band 6, p. 298.

**B. *Free Mineral Acids.***

According to the investigations of C. Gaethgens\* dilute sulphuric acid after long use goes over into the urine partly in an uncombined state.

**C. *Salts of the Alkalies.***

1. Carbonates of the alkalies always appear again as such in the urine, although a portion is necessarily neutralized by the free acid of the gastric juice. They render the urine either neutral or alkaline. Free carbonic acid, sparkling wines, beer, and acid alkaline carbonates cause an increased excretion of calcic oxalate, and at the same time increase the amount of free carbonic acid in the urine.

2. Lithium salts, after their internal use, very readily go over into the urine.

To detect the lithium a sufficient amount of the urine to be examined is evaporated to dryness and the residue heated at a moderate temperature to complete ignition. After cooling, the carbon is extracted with dilute hydrochloric acid, filtered, the colorless filtrate evaporated to dryness, treated with strong alcohol, filtered, the alcoholic solution evaporated to dryness, and the residue now left is tested with the spectroscope. I have always succeeded in detecting lithium, after its internal use, with absolute certainty according to the above method.

3. Ammonium salts pass into the urine in part unchanged.

I have made experiments on this point with a young man twenty years of age, who passed on an average of twelve determinations 0.6137 grams of ammonia in twenty-four hours, corresponding to 1.9305 grams of ammonic chloride. Of a solution, which in ten cc. contained exactly two grams of ammonic chloride, ten cc. were taken in the evening in a glass of water, the urine was collected for exactly twenty-four hours and submitted to analysis. The experiments were continued for five days, and during this time, if we deduct the above-mentioned normal amount, 9.957 grams of ammonic chloride were eliminated again instead of the ten taken.

4. Ferrocyanide of potassium appears in the urine reduced to the ferricyanide.

5. Sulphocyanide of potassium appears quickly in the urine even after taking small amounts.

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\* Centralblatt f. d. med. Wissenschaft., 1872, No. 53.

6. Alkaline silicates, chlorates, and borates are found again in the urine.

7. Perchlorate of potassium, according to Rabuteau, readily appears in the urine.

To detect it the urine is completely precipitated with nitrate of silver, the excess of silver is removed from the filtrate by sodic hydrate, filtered again, evaporated to dryness, and the residue ignited. The perchlorate of potassium present thus becomes converted into the chloride of potassium, whose amount can easily be determined in the usual way.\*

8. Iodide of potassium also passes into the urine and is readily detected by the familiar starch reaction.

Pierre Scivoletto moistens strips of filter paper with starch paste, sprinkles them after drying with the urine to be tested for iodine, and then suspends them in the upper part of a flask, at the bottom of which there is a little fuming nitric acid. If iodine is present, the sprinkled spots become colored blue. The following method used by Castain might be more accurate when very small amounts of iodine were present: About one liter of the urine is treated with two grams of caustic potash, evaporated to dryness, and all of the organic matter ignited. The residue is dissolved in water and tested for iodine with starch and chlorine water or fuming nitric acid.

A concentrated solution of hyponitric acid in sulphuric acid is suitable to free the iodine. Or it may be set free by the careful addition of bromine water, and removed by shaking with bisulphide of carbon. I prefer the last reaction to all others.

9. Bromide of potassium passes into the urine readily.

To detect it the residue of the urine is carefully but completely carbonized. The carbon is extracted with water, the bromine present in the colorless filtrate is freed by a drop of chlorine water, and the mixture shaken with ether or bisulphide of carbon in the usual manner. For the quantitative estimation Caigniet uses a standard solution of hypochlorite of sodium. The colorless filtrate is acidulated with citric acid and the standard solution carefully added from a burette. The freed bromine is taken up with bisulphide of carbon which is renewed from time to time. A colorless fluid always results,

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\* *Zeitschrift f. analyt. Chem.*, Band 8, p. 233.

and it is easy to hit the point at which another drop of the hypochlorite of sodium solution causes no more coloration of the fluid and of the bisulphide of carbon, by which the end of the experiment is indicated.\*

10. Sulphide of potassium escapes again partly as sulphate, and partly unchanged.

*D. Salts of the Alkaline Earths.*

1. Soluble barium salts can be detected in the urine when they have been taken in pretty large doses.

2. Lime salts do not pass into the urine at all, or at most only in very small amount. On the contrary, S. Soborow † observed a considerable increase in the amount of lime in the urine after large doses of the carbonate (8 to 10 grams in a day). After taking eight grams of carbonate of calcium the amount of lime in the urine increased from 0.216 to 0.73 grams, and after the internal use of ten grams of the carbonate there was an increase of 0.27 to 0.87 grams. An increase of lime in the urine was also obtained in a dog after the subcutaneous injection of one gram of the acetate of calcium.

3. Magnesium salts are partly eliminated with the urine. (Kerner.)

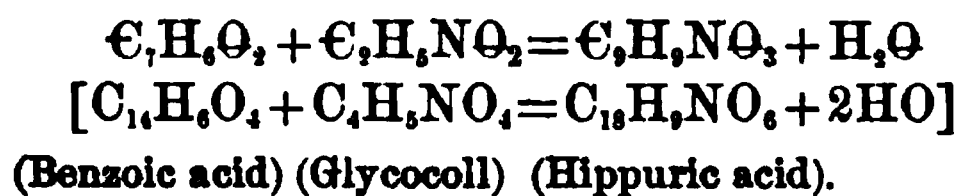
## II. ORGANIC SUBSTANCES.

*A. Free Organic Acids.*

1. Organic acids, such as oxalic, citric, malic, tartaric, and gallic acids, according to Wöhler, pass into the urine unchanged when they are presented to the economy in a free state.

2. Acids of the Aromatic Series.

a. Benzoic acid becomes converted into hippuric acid in the economy by combining with a molecule of glycocoll and eliminating a molecule of water.



Benzoic ether, oil of bitter almonds, cinnamic, quinic, and mandelic acids are also transformed into hippuric acid, and

\* Zeitschrift f. analyt. Chem., Band 9, p. 427.

† Centralblatt f. d. med. Wissenschaft., 1872, Nr. 89.



appear as such in the urine. (Frerichs and Wöhler; Erdmann and Marchand; Lautemann; O. Schultzen, and C. Gräbe.)

Nitrobenzoic acid yields nitrohippuric acid. (Bertagnini)  
Chlorobenzoic acid yields chlorhippuric acid. (O. Schultzen and C. Gräbe.)

b. Toluic acid ( $\beta$ ) appears in the urine as toluric acid (Kraut); salicylic acid in part as salicyluric acid (Bertagnini); anisic acid as anisuric acid (O. Schultzen and C. Gräbe). These acids stand in the same relation to the original that hippuric acid does to benzoic. Also, after the internal use of mandelic acid, a hippuric acid, corresponding to mandelic acid, appears in the urine. (O. Schultzen and Gräbe.)

c. Experiments with phtalic, amidobenzoic, cuminic, and cumarinic acids led to no decided results.

d. Oxybenzoic and paraoxybenzoic acids, the known isomers of salicylic acid, according to the investigations of Maly \* do not take up simple glycocoll in the organism, but methyl- or ethylglycocoll, and then appear in the urine as methylated or ethylated hippuric acid.

e. Salicylic acid, as already mentioned above, goes over only in part as salicyluric acid, another part passes from the economy unchanged. After the internal use of 0.3 gram of salicylic acid it could be detected in the urine in two hours, but was still present after twenty hours. (Kolbe.)

To test urine for unchanged salicylic acid it is treated with a solution of ferric chloride drop by drop. The first drop of an iron solution always causes an abundant separation of white phosphate of iron, but as soon as this is precipitated the intense violet reaction with salicylic acid appears on further addition of the iron salt.

O. Schultzen and C. Gräbe † from their investigations of this subject draw the conclusion that all aromatic acids in which the group  $\text{CHO}$ , directly replaces one atom of hydrogen in benzol, are transformed in the economy to the corresponding hippuric acid, while in those acids which contain a complicated side chain, as cinnamic and mandelic acids, this side chain becomes oxidized, so that the hippuric acid corresponding to

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\* Jahresbericht üb. d. Fortschritte der Thierchemie, 1872, p. 137.

† Annalen d. Chemie u. Pharm., Band 142, p. 345. Reichert's und Du Bois-Reymond's Archiv, 1867, Heft 2.



the one ingested does not appear in the urine, but that corresponding to the product of its oxidation; consequently all aromatic acids yield in the economy so-called hippuric acid, that is, glycocoll substitution products.

3. Pyrogallic acid, which, according to G. Jüdel,\* in large doses has an intensely poisonous action, goes over into the urine undecomposed.

4. Tannic acid is changed to gallic acid and appears as such in the urine.

5. Camphoric acid is eliminated unchanged with the urine.

6. Succinic acid was found again in the urine. (Meissner and Shepard.)

Considerable amounts of succinic acid occurred after partaking largely of asparagus. Here it was evidently formed by the decomposition of the asparagin (amidosuccinaminic acid) in contact with ammonia.

7. Uric acid undergoes the same decompositions in the economy which we are able to produce artificially by the action of peroxide of lead, or better still, of permanganate of potassium. In the perfectly normal organism, when the respiration is unimpeded, uric acid is decomposed by the absorption of water and oxygen for the most part into urea and carbonic acid.

When the respiration is more or less disturbed, oxalic acid accompanies the above products of decomposition, and under certain circumstances allantoin also, which Städeler and Freichs saw really occur in artificially disturbed respiration. (See Uric Acid, § 6, D, 3 and 5.)

8. After taking abietic acid or other resins, such as turpentine, balsam copaiba, etc., according to Maly, abietate of sodium is eliminated with the urine. In such a urine a white cloudiness, not unlike a precipitation of albumen, is produced by nitric acid, which, however, immediately disappears on the addition of alcohol.

#### B. *Indifferent Substances.*

1. Alcohol. According to the investigations of Lieben,† alcohol is constantly eliminated in the urine after partaking of spirituous drinks, and can be separated by fractional distilla-

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\* Hoppe-Seyler, Med. chem. Untersuchungen, Heft 3, p. 422.

† Annal. d. Chem. u. Pharm., 7, Supplementbd., p. 236.

tion, yet the amount of alcohol which appears in the urine is always relatively small, both after small and large doses.

2. Phenol (carbolic acid) appears in the urine after both its external and internal use, and, according to Waldenström and Almén, Salkowski, and others, may be readily detected in the distillate of the urine acidulated with sulphuric acid by means of the usual reactions.\* It is well to shake the distillate obtained with ether, evaporate the ether, and test the residue for phenol. (§ 9, C.)

3. Chloroform is eliminated with the urine, and such a urine reduces Fehling's copper solution on heating. To detect and estimate it quantitatively, according to Maréchal, a stream of air is forced through the urine to be examined, and, saturated with chloroform, is conducted through a red-hot porcelain tube. The chlorine, which by this process is set free from the chloroform, will precipitate chloride of silver on being passed through a Liebig's bulb tube filled with nitrate of silver solution, and from the weight of the chloride the amount of chloroform which was present may be calculated.†

4. Chloral, according to the investigations of von Mering and Musculus,‡ is eliminated unchanged in the urine to a very small extent, but by far the greatest part combines with constituents of the economy, and appears in the urine as urochloralic acid ( $C_7H_5ClO_6$ .)

After taking chloral (five to six grams) the urine has a strong acid reaction and reduces an alkaline solution of copper. The detection of chloroform or formic acid in the urine did not succeed, but on the other hand small quantities of chloral were detected by means of Hofmann's isocyanphenyl reaction. Sugar was not present, but a not inconsiderable amount of an organic acid which turned a ray of polarized light to the left, and to which von Mering and Musculus have given the name urochloralic acid, was detected.

Urochloralic acid is separated by the following treatment: The urine containing chloral is evaporated on the water bath, treated with sulphuric acid, and shaken with a mixture of two volumes of ether and one volume of alcohol. The ether is dis-

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\* Zeitschrift f. analyt. Chem., Band 10, p. 125.

† Zeitschrift f. analyt. Chem., Band 7, p. 898 und Band 8, p. 99.

‡ Berichte d. deutsch. chem. Gesellschaft, Band 8, p. 662.

tilled off, the residue neutralized with potassic hydrate, evaporated, taken up with 90 per cent. alcohol, filtered, the filtrate precipitated with ether, the precipitate dissolved in water, decolorized with animal charcoal, and evaporated to a small volume. On cooling a crystalline mass separates, which for the most part consists of the potassium salt of urochloralic acid. By washing the salt, which has been dried over sulphuric acid, with absolute alcohol, it is freed from the urea and hippurate of potassium which are mixed with it. The pure potassium salt is then dissolved in as little water as possible, acidified with hydrochloric acid, this solution shaken with the mixture of ether and alcohol above mentioned, and filtered. Most of the chloride of potassium remains on the filter, and the rest separates if the filtrate is treated with a great excess of ether, and is allowed to stand forty-eight hours. The filtrate is evaporated and the residue freed from chlorine by moistened oxide of silver. The excess of silver oxide which has gone into solution is quickly precipitated by sulphuretted hydrogen, and the filtrate evaporated to a syrupy consistence. The acid crystallizes after twelve hours. The potassium salt gave 12.56 per cent. of potassium; the barium salt 19.57 per cent. of barium.

Urochloralic acid crystallizes in colorless silky needles, which have a starlike arrangement like tyrosin, and readily dissolve in water, alcohol, and a mixture of alcohol and ether, but are insoluble in ether. On boiling it reduces an alkaline solution of copper, silver, and bismuth, and colors yellow a solution of indigo made feebly alkaline with carbonate of sodium. Its solution turns the plane of polarization toward the left, and indeed the specific power of rotation of the potassium salt for yellow light was found to approximate  $(\alpha) = -60^\circ$ . The urine, after the introduction of five to six grams of chloral hydrate into the organism, turned polarized light about  $5^\circ$  to the left; it contained, therefore, about ten grams of this acid in the liter. Urochloralic acid on heating with anilin and an alcoholic solution of potassic hydrate evolved no isocyanphenyl.

##### 5. Hydrocarbons of the Benzol Series.\*

a. Benzol is oxidized in the system and appears in the urine again as phenol (carbolic acid).

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\* O. Schultzen u. B. Naunyn, Reichert's u. Du Bois-Reymond's Archiv, Jahrg. 1867, Heft 3.

b. Toluol is oxidized to benzoic acid in the economy, and appears in the urine as hippuric acid.

c. Xylol in the system is first oxidized to toluylic acid, and appears in the urine as toluric acid.

d. Camphorcymol ( $C_{10}H_{14}$ ) after its internal administration is converted into cuminic acid (propylbenzoic acid) according to the investigations of Nencki and Ziegler.\*

To separate these acids the urine is treated with an amount of subacetate of lead which is insufficient to completely precipitate it, it is filtered, the filtrate concentrated to a syrup, precipitated with alcohol, the alcoholic solution evaporated, acidulated with dilute sulphuric acid, and shaken with ether. The ether leaves an acid oil behind, which solidifies after long standing. It is saturated with carbonate of barium, treated with animal charcoal, and the concentrated filtrate treated with hydrochloric acid, which separates the acid in crystals which are purified by recrystallization.

e. Mesitylen (trimethylbenzol), according to Nencki,† readily becomes converted into mesitylenic acid in the economy, and is eliminated in part as such, and in part united with glycoll as mesitylenuric acid. Both can be separated by distillation with aqueous vapor, during which the volatile non-nitrogenous acid passes over and deposits in the receiver.

f. Nitrotoluol has an excessively poisonous action. Paranitrotoluol, which in dogs, at least, manifests no poisonous action, becomes paranitrobenzoic acid to a very slight extent, and is found in the urine as such. The largest part of the paranitrotoluol, on the other hand, is transformed into paranitrohippuric acid and appears in the urine as paranitrohippurate of urea. (Jaffé.)‡

### C. *Salts of the Organic Acids.*

1. Neutral salts of the alkalies with the vegetable acids are oxidized in the economy just as if they were consumed in oxygen gas. They appear in the urine as carbonates, therefore, render it alkaline, cause an effervescence with acids and a separation of the earthy phosphates. If the salts at the same time

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\* Berichte der deutsch. chem. Gesellschaft, 1872, p. 749.

† Archiv f. experim. Pathol. u. Pharmakol., 1878, p. 420.

‡ Berliner Berichte, Band 7, p. 1678.

have a purgative action, or if they are taken with much animal food, the urine in the former case is often not at all, and in the latter only slightly alkaline. Moreover, other circumstances, especially certain diseases, exercise an influence on these ordinary appearances.

2. The ethereal sulphates of sodium, according to the investigations of E. Salkowski,\* pass over into the urine unchanged.

Para- and meta-sulphophenate of sodium likewise leave the economy unchanged. After the internal use of these salts the urine is colored deep blue after the addition of a trace of ferric chloride, as happens with phenolsulphuric acid.

Benzol sulphate of sodium provoked much diarrhoea in dogs, and could not be detected in the urine. The urine contained benzolsulphuric acid unchanged after the injection of two grams under the skin.

#### D. *Organic Bases, etc.*

1. Quinine can be easily found in the urine after the administration of not too small doses.

a. According to the interesting investigations of Kerner,† quinine can be most easily and surely detected in the urine, even when diluted two million times, by means of its fluorescent properties. Since, however, the chloride of sodium which is present prevents the fluorescence, the chlorine must be removed first, which is done most efficiently by means of a concentrated solution of mercurous nitrate. Twenty-five to fifty cc. of urine are treated with the reagent until a precipitate no longer takes place and there is a slight excess of the reagent present, it is filtered and the precipitate washed. Of the original color of the urine only a pale yellow is left, and when not too small amounts of quinine are present, the fluorescence can be perceived by daylight during the filtration. If the fluid is placed in the fluorescope constructed by Kerner and represented in fig. 7, the fluorescence will be seen most beautifully, even at a dilution of two million times, as soon as the induction current passes through the Geissler fluorescence-tube, and the cover is closed, if the observation is made through the pyramidal tunnel. For the sake of comparison it is well to fill only one

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\* Pflüger's Archiv, Band 4, p. 91.

† Archiv f. Physiologie, Band 2, p. 200. Zeitschrift f. analyt. Chem., Band 9, p. 134 im Auszug.

arm of the U-shaped tube with the urinary fluid, and the other with water. The reaction is still more delicate if the urinary

FIG. 7.

fluid is completely decolorized before testing; this is done most simply by conducting a few bubbles of sulphuretted hydrogen into it, when the sulphide of mercury takes up the rest of the coloring matter.

Hera path gives the following method for the same purpose: The urine is rendered alkaline with a little potassic hydrate; it is shaken with ether, which takes up the quinine, after which the ether is evaporated. Then a test fluid is prepared of three drachms of acetic acid, one drachm of rectified spirit, and six drops of dilute sulphuric acid. One drop of this mixture is put on a glass slide, a little of the ether residue is added to it, and then a very small drop of an alcoholic solution of iodine is brought in contact with it by means of a glass hair. If quinine is present, a cinnamon color appears immediately, caused by the iodide of quinine, and later sulphate of iodo-quinine is obtained, which is remarkable for its polarizing properties, and which is recognized under the microscope. Sulphate of iodo-quinine crystallizes in extremely thin plates, whose power of polarization is so strong that they can be used instead of tourmaline plates. Two plates as thin as gold leaf, when they cross each other at a right angle, allow no light to pass through.\*

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\* Journ. f. pract. Chem., Band 96, p. 87.

According to Binz, quinine can be detected in urine, when present in the proportion of one part to 40,000 or 50,000 parts of urine, by means of a solution of two parts of iodine and one part of iodide of potassium in forty parts of water.\*

b. By the method of Vitali and E. Salkowski, the urine is made alkaline with ammonia and shaken with ether. After the addition of a drop of hydrochloric acid the ether is evaporated, the residue is dissolved in water, rendered ammoniacal again, and this solution shaken with ether a second time. The residue which now remains, after the evaporation of the ether, is used for the familiar reaction with chlorine water, and ammonia.

2. Thein and theobromin cannot be detected again in the urine.

3. Anilin was not found again by Wöhler.

4. Alloxantin, according to Wöhler, appears to break up into urea and other substances.

5. Allantoin does not pass into the urine; it also causes no increase of the calcic oxalate, but is probably decomposed into carbonic acid and urea.

6. Urea passes off with the urine again unchanged.

7. Guanin causes a considerably increase of the urea, but in very large doses it passes off partly with the fæces.

8. Glycocoll and leucin, even when taken into the economy in large doses, are eliminated again in the form of urea.†

9. Sarkosin changes in the economy partly to methylhydantoic acid, and partly takes up the sulphamic acid group and appears in the urine as a body containing sulphur. Two well-characterized bodies appear in the urine after taking a sufficient amount of sarkosin, which, on heating with hydrate of barium, decompose into carbonic acid, ammonia, and sarkosin, or sulphuric acid, ammonia, and sarkosin. (Schultzen.)‡

Schultzen obtained these compounds from the urine by the following procedure: The urine passed within the next two hours after their ingestion was completely precipitated by basic acetate of lead, the filtrate was shaken with oxide of sil-

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\* *Zeitschrift f. analyt. Chem.*, Band 9, p. 588.

† O. Schultzen und Nencki. *Bericht d. deutschen chem. Gesellschaft*, 1869, p. 566.

‡ *Berliner Berichte*, Band 5, p. 578.



ver, it was filtered off from the excess of oxide and chloride of silver, and treated with sulphuretted hydrogen. The filtrate from the metallic sulphides was evaporated to a syrup, treated with dilute sulphuric acid in excess, and frequently shaken with large amounts of ether. The ether left a colorless syrup which contained both bodies. By boiling with carbonate of barium and precipitating the concentrated solution with absolute alcohol, the barium salt of the compound of sarkosin with sulphamic acid separates, while the alcoholic solution after evaporation leaves as a residue the carbamic acid derivative in magnificent tabular crystals as clear as glass.

According to recent investigations by Baumann, von Mering,\* and Salkowski,† sarkosin for the most part leaves the economy unchanged and appears as such in the urine again. But since methylhydantoic acid readily becomes methylhydantoin by the separation of water, Salkowski considers that the occurrence of this body in the urine is possible after taking sarkosin. Lastly, a part of the sarkosin (methylglycocoll) may be changed into methylurea, just as glycocoll changes into simple urea.

Moreover, it must be mentioned that, according to the investigations of Hoppe-Seyler and Baumann, methylhydantoic acid is readily formed, if sarkosin is warmed a long time with urea and an excess of baryta.

Sarkosin can be detected in urine which has been first treated with basic acetate of lead, then freed from the excess of lead, evaporated, and fractional precipitation made with alcohol or rather a mixture of alcohol and ether. By treating with hydrate of copper, well-crystallized sarkosin-copper is produced. If this is dissolved in water to which has been added a drop of hydrochloric acid, the copper precipitated with sulphuretted hydrogen, and the hydrochloric acid with oxide of silver, the filtrate yields crystals of sarkosin after evaporation. (Salkowski.)

10. Taurin behaves in a similar manner in the economy. A small portion goes over into the urine unchanged, the largest portion takes up the carbamic acid group and appears in the urine as taurocarbamic acid, which crystallizes in shining quad-

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\* Berichte d. deutsch. chem. Gesellschaft, Band 8, p. 584.

† Berichte d. deutsch. chem. Gesellschaft, Band 8, p. 688.



rilateral leaflets, and on being treated with baryta water at 130° or 140° C. decomposes into carbonic acid, ammonia, and taurin. This acid can be produced artificially from taurin and cyanate of potassium at a gentle heat. (Salkowski.)\*

To detect taurin in the urine it is precipitated with basic acetate of lead, filtered after standing several hours, the filtrate freed from lead with sulphuretted hydrogen, evaporated and precipitated with absolute alcohol. The alcohol is quickly poured off from the precipitate which has taken place, and left at rest, when after twelve to twenty-four hours the taurin will separate in a crystalline form.†

11. Acetamid leaves the body rapidly and unchanged.‡

12. Amygdalin cannot be found again with certainty, but the urine, according to Lehmann and Ranke, contains considerable quantities of formic acid.

13. Salicin is decomposed as if by oxidizing agents. The urine contains salicylic hydride, salicylic acid, and saligenin, but no sugar and no phenylic acid.

14. Santonin. After using santonin the urine resembles one containing biliary coloring matter. A characteristic is that the yellow or greenish color of the urine becomes a cherry red or purple red after the addition of potassic hydrate. The color does not disappear on boiling, but it does on the addition of acids, and is restored again by alkalies. According to Mialhe this coloring matter appears to be a product of oxidation, since santonin on boiling with nitric acid gives a solution which exhibits a green color after dilution with water, and which changes to an orange red after the addition of potassic hydrate.§

15. Strychnia, according to O. Schultzen, and morphia, according to the experiments of Bouchardat and Dragendorff,| even in large amounts, pass into the urine.

16. Veratria, according to Masing,¶ passes into the urine in considerable amount.

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\* Berichte der deutsch. chem. Gesellschaft, Band 6, p. 1191.

† Salkowski, Virchow's Archiv, Band 58, p. 460-502.

‡ O. Schultzen and Nencki, loc. cit.

§ Natta und Smith. Zeitschrift f. analyt. Chem., Band 4, p. 404, und Band 10, p. 254.

| Pharm. Zeitschrift f. Russland, 1868, Heft 4.

¶ Zeitschrift f. analyt. Chem., Band 8, p. 240.

17. Asparagin (amidosuccinamic acid) does not pass into the urine unchanged. It decomposes in the economy into succinic acid and ammonia, both of which appear in the urine. (Hilger.)

At the same time, after taking asparagin, as well as asparagic acid, the amount of urea is increased in the urine. (Von Knieriem.)

18. Indol after its subcutaneous injection becomes converted into indican, and appears as such in the urine. (Jaffé, Nencki, and Masson.)

Oxindol and dioxindol become changed into red coloring matters, which resemble those obtained by the oxidation of aqueous solutions of oxindol and dioxindol in the air. (Nencki and Masson.) See page 69.

19. After taking isatin the urine contains a coloring matter which in all of its properties corresponds with indigo red (urrhodin). (R. Niggeler.)

To detect alkaloids in the urine the same methods are to be used which are employed in legal cases to separate these substances.\*

*E. Coloring and Odorous Matters.* Most coloring and odorous matters pass into the urine unchanged or but slightly modified. Wöhler found in the urine the pigments of indigo, madder, gamboge, rhubarb, logwood, turnips, and bilberries, besides the odorous matters of the valerian, garlic, assafoetida, castor, saffron, and turpentine. On the contrary, he did not find camphor, resins, empyreumatic oils, musk, ether, cochineal, litmus, sap-green, and alkanet coloring matter.

On the other hand, according to investigations of R. Niggeler,† indigo blue passed through the intestinal canal unchanged and caused no increase of the indican in the urine.

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\* Fresenius, *Qualitative Analyse*, 18<sup>te</sup> Aufl., p. 458.

† *Jahresbericht f. Thierchemie*, Band 4, p. 220.

## DIVISION SECOND.

### QUANTITATIVE ESTIMATIONS.

#### § 57. ESTIMATION OF THE AMOUNT OF URINE SECRETED IN A GIVEN TIME.

It must be remembered that the determination of the amount of urine passed in a given time is the basis of all other quantitative estimations, and should not be neglected in any case. Therefore, the amount of the urine, and the time during which it was passed, must be annexed to every analysis of urine. These determinations can be made either with the balance or by measuring, yet only the latter method is now in general use.

For this purpose the cubic centimeter, one thousand of which are equal to one liter (1 liter = 2 pounds, or 1,000 grams of water), always serves as the unit of measure. If at the same time we know the specific gravity of the urine, the amount of which has been determined by measurement, it can be readily expressed by weight, since it is only necessary to multiply the number of cubic centimeters found by the specific gravity of the urine; 1,000 cc. of urine of 1.030 sp. gr., therefore, weigh 1,030 grams.

The measurement of the amount of urine should always be made in graduated glass cylinders, several of which, small and large, should be at hand.

1. To determine the amount of urine of twenty-four hours a measuring vessel which holds at least 2,000 cc. (2 liters), and is graduated into 100 cc. divisions, is needed. Such a one may be easily prepared by accurately weighing into a preserve jar of the proper size 100 grams of water, and carefully marking the position of the fluid with a file or diamond; then 100 grams of water are again weighed into it and the point marked

again; this process is continued until the whole glass is graduated up to 2,000 or 3,000. This vessel can be used directly for collecting the urine in twenty-four hours; it must be carefully covered with a glass plate, however, on which a thin layer of tallow, or, better still, wax, has been spread, and kept in a cool place, so that there shall be no evaporation of water in the first place, and in the second, that the decomposition of the urine shall not be hastened by heat. With these vessels it is necessary to judge of the amount between each 100 cc., so that an error of 10 to 20 cc. may occur; if we wish to avoid this, the urine must be collected in another vessel, and then the measuring glass filled exactly to a file-mark, and the rest measured off in a smaller graduated cylinder.

2. To determine the amount of urine secreted during a short but definite time, finely graduated cylinders with a foot are better; such a one holds 200 to 300 cc., and must be divided into single cubic centimeters. (Fig. 8.) They serve for determining the amount of urine for each hour very accurately.

FIG. 8.

According to the object of the examination, sometimes the first, and sometimes the second determination is made; and it is to be remarked that the collection of twenty-four hours is better suited to observe large, long-continued differences in the secretion of urine, and is, therefore, used in most investigations of disease. The determination of the amount of urine passed in a short time, however, allows transient differences in the secretion to be observed, and is, therefore, better adapted for studying the action of transient influences on the urinary secretion.

Lastly, we must mention that the urine must be collected and analyzed several days in succession in all examinations in which it is desirable to obtain an average value, and the mean of the results thus obtained must be taken.

#### § 58. SPECIFIC GRAVITY.

1. *By the Aræometer (Urinometer).* Although only approximate results can be obtained for the true specific gravity of a urine by means of an aræometer, yet its use is perfectly legiti-

mate for a physician's purposes. Such an aræometer should allow the specific gravity of the urine to be accurately determined between 1.000—the sp. gr. of water—and at least 1.040—about the highest sp. gr. which human urine reaches—even to half a degree; then it ought not to be too large, so that it may serve for small amounts of urine also. To obtain the greatest possible accuracy with these instruments, it is well to divide the specific gravities of 1.000 to 1.040 on two aræometers, so that one shall run from 1.000 to 1.020, and the other from 1.020 to 1.040; the possibility will then be attained of being able to determine halves and quarters of a degree.

All instruments of this sort, however, only give correct results at a stated temperature for which they are constructed; if, therefore, we wish to be very accurate, it is first necessary before testing to bring the urine to this temperature. According to some experiments by Siemon, the specific gravity of a urine which at  $+12^{\circ}$  C. was 1.021, at  $+15^{\circ}$  C. sank to 1.020, and at  $+18^{\circ}$  C. to 1.019, so that a difference of temperature of  $3^{\circ}$  C. corresponds to about a degree of the urinometer.

FIG. 9.

Beneke arrived at the same results.

At my request, Mr. Niemann, of Alfeld (Germany), now constructs urinometers which are furnished with a small thermometer in the float, on which the normal temperature at which the apparatus is constructed is designated by a red line. The scale on these urinometers is considerably longer than those made by Greiner of Berlin (Germany). The single degrees are large, distinct, and marked with black marks, while the half degrees are marked quite distinctly with red lines, so that an accurate reading is very much facilitated. I have had for some time two such urinometers in use and am pleased in every respect with them, and therefore recommend them to those who are engaged in urinary analysis. (Fig. 9.)

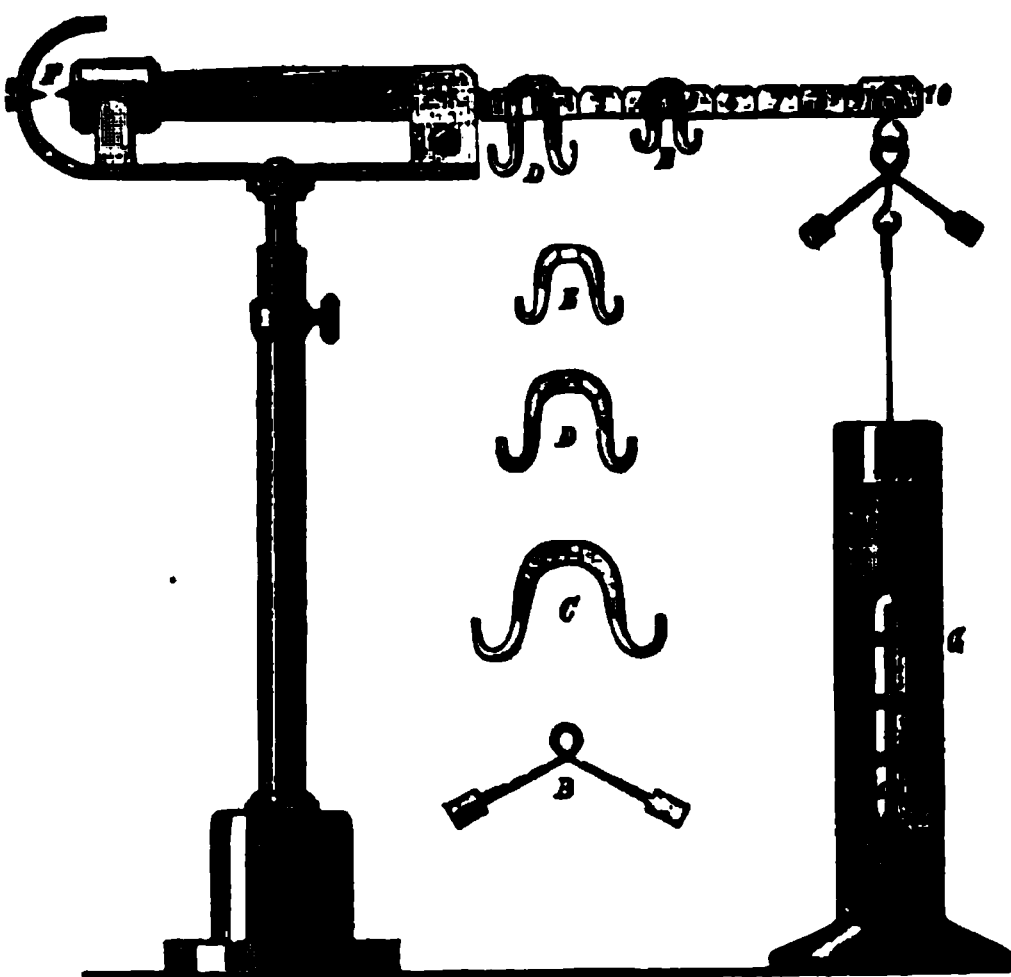
To determine the specific gravity with an aræometer, a suitable upright cylinder is four-fifths filled with the clear filtered urine, all bubbles of air are removed with a glass rod, or better with blotting paper, and the clean instrument is then slowly introduced into it. The cylinder

must necessarily be of such a width that the urinometer can freely float in the fluid and not touch the sides of the glass at any point. The reading is accomplished most accurately when the eye is brought to a level with the lower part of the surface of the fluid, and this is accomplished when the posterior edge of the surface of the fluid can no longer be seen; the point at which the plane of the fluid cuts the urinometer scale is the one which should be read off. When it is not rightly held before the eye, either too low or too high, the surface of the fluid appears to be in the form of an ellipse. The aræometer is then pressed a few degrees deeper into the urine, allowed to come to rest, and then read off a second time as a correction. Carried out in this way, the results with a good aræometer, such as Niemann furnishes, are very accurate. The aræometers of Greiner, of Berlin, have too short scales.

2. *With the Mohr-Westphal Balance.* This ingenious and accurate instrument for determining the specific gravity depends on the principle that the loss of weight which the same body

FIG. 10.

suffers in different fluids is proportional to the specific gravity of the fluid. On one arm of the balance, fig. 10, the glass sinker A, which has the form of a small thermometer, hangs by means of a fine platinum wire, and is exactly equipoised by the other arm of the balance. The arm of the balance, on which the glass sinker A hangs, is divided into ten equal parts. B, C,



D, and E represent the forms of the weights, made of brass and aluminium, which belong to it. The weights B and C each weigh exactly as much as the loss of weight  $v$ , which the glass sinker A suffers in water, while D is exactly one-tenth of this

loss of weight, and the weight E made of aluminium weighs exactly one one-thousandth of  $v$ .

If the specific gravity of the urine is to be determined with this balance, the glass cylinder G, in which the sinker hangs, is filled with it. The weights are then so placed that the lever stands perfectly horizontal, when the sinker is wholly immersed; this is readily determined by the two points at F.

For example, if the weight B must be hung on the division 10 of the lever, the weight D, which is ten times lighter on the division 2, and the aluminium weight E, which is one hundred times lighter on the division 5 in order to restore the equipoise, the specific gravity of the urine is 1.025.

The mechanician Westphal in Celle (Hanover, Germany) furnishes these balances of most excellent workmanship at very moderate prices.

3. *With the Picnometer.* This method is grounded on the fact that the specific gravity of a fluid is obtained by dividing the absolute weight of a given volume of the fluid examined by the absolute weight of an exactly equal volume of distilled water. For this purpose a glass with as thin walls as possible, closed with a ground-glass stopper, carefully cleaned and dried, and holding 40 or 50 cc., is weighed on a fine chemical balance, first while empty, and its weight noted. It is then filled perfectly full with distilled water and all of the air bubbles are carefully removed, the stopper is put in air-tight, and if no bubbles are seen, the flask is carefully dried on the outside, first with a linen cloth and then with blotting paper, and it is again weighed. If the weight of the empty glass already known is subtracted from this weight, the exact absolute weight of the volume of distilled water which the glass can contain is obtained. The weight of this amount of water as well as the temperature at which it was obtained is noted once for all.

If it is desired to ascertain the specific gravity of a urine, the empty glass is repeatedly rinsed out with it and then filled with the urine, observing the above precautions, closed, carefully dried as mentioned above, and the weight determined; from this gross weight that of the empty flask is subtracted, and the absolute weight of the urine is thus obtained, which corresponds exactly to the volume of distilled water found in the first experiment. From these data the specific gravity of the urine

is readily reckoned, since it is only necessary to divide its absolute weight by that of the distilled water already known, in order to obtain as a quotient the specific gravity of the urine in question.

An example may serve to explain this:

The flask with distilled water weighs	80	grams.
The flask alone	30	“
<hr/>		
It therefore holds	50	“ of water.
The flask with urine weighs	81.2	“
The flask alone	30.0	“
<hr/>		
It contains, therefore,	51.2	“ of urine.

The specific gravity of the water = 1.000.

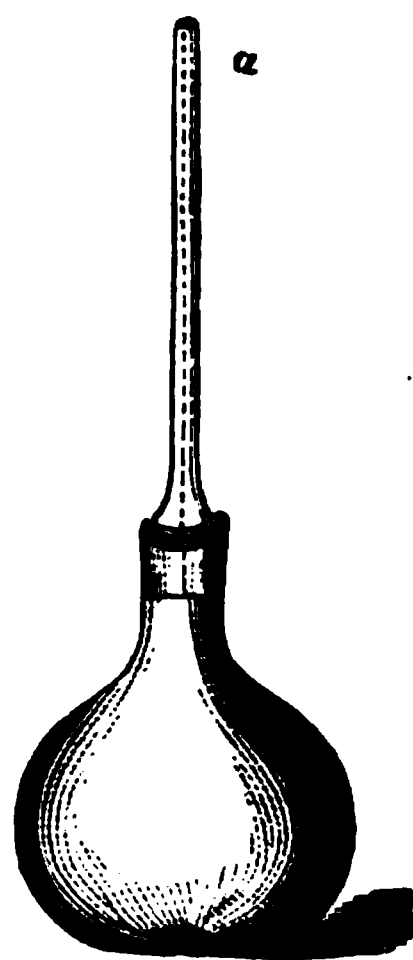
We then have the proportion :

$$50 : 51.2 = 1.000 \text{ (sp. gr. of water)} : x \text{ (sp. gr. of the urine).}$$

$$\frac{51.2 \times 1.000}{50} = 1.024.$$

Instead of an ordinary flask it is better to use the picnometers made for this purpose (fig. 11), which have many advantages. These glasses are easy to weigh, they hold a tolerably large amount of fluid, and obviate the shutting in of air bubbles, since the latter can escape through the fine capillary tube in the ground tube-stopper *a*. Perfectly complete picnometers have a small thermometer in this tube, by means of which the temperature may be determined at the same time. The calculation is just the same as above; the weight of the distilled water which the picnometer can hold is determined once for all.

FIG. 11.





§ 59. ESTIMATION OF THE WATER AND OF THE TOTAL SOLIDS  
IN SOLUTION.

In the estimation of the solid residue of urine many difficulties stand in the way, which are caused in the first place by the readiness with which the urine decomposes, and secondly by the very hygroscopic character of the residue. According as greater or less accuracy is required, sometimes the first and sometimes the second method is chosen.

1. Ten to fifteen grams or cc. of urine are weighed or mea-

FIG. 12.

sured into a rather small accurately-weighed porcelain crucible (fig. 12), which can be closed with a cover, and evaporated to dryness over the water bath.

FIG. 13.

Instead of a

crucible a small glass cup with a ground edge which can be hermetically sealed by means of a ground-glass plate (fig. 13) may be used. Naturally the residue cannot be ignited in this vessel. (§ 60.)

A water bath adapted to all of these purposes is shown in figure 14. It is made of strong sheet copper, and when in use

FIG. 14.



is half filled with water, which is kept at the boiling point by means of a small spirit lamp. It is furnished with rings of different sizes for evaporating dishes and crucibles of various diameters; these rings are

simply laid on the top. The diameter from *a* to *b* is from four to six inches.

The residue thus obtained is not yet entirely freed from water, and must, therefore, be dried a still longer time at 100° C. The air bath, figured in the adjoining cut (fig. 15), will serve for this purpose. The crucible containing the evaporated residue is placed in the wire frame *c*, and the apparatus heated with a small spirit lamp placed underneath. By means of a thermometer *d*, fastened in with a stopper at the hole *c*, the

temperature is determined, and can easily be kept constant with very slight variations.

After the urinary residue has been dried in this manner one or two hours, the crucible is covered and allowed to cool in a desiccator over concentrated sulphuric acid, since its contents would attract water again from the air with great eagerness; fig. 16 represents such an apparatus, in which *b* is a holder made of lead wire on which the crucible is placed. The vessel is hermetically sealed by a glass plate smeared with tallow. The crucible is carried to the scales in this

FIG. 15.

FIG. 16.



apparatus and weighed quickly. It is now for a second time exposed for a while to a temperature of  $100^{\circ}$  C. and weighed again; if it has not considerably decreased in weight, the operation is finished, and after subtracting the weight of the crucible the amount of residue is obtained, and is reckoned for the whole quantity of urine.

If, further, the weight of the residue is subtracted from that of the quantity of urine taken, the remainder is the amount of water evaporated.

Example:

I. Amount of urine in twenty-four hours = 1,000 cc. of a sp. gr. 1.025. Ten cc. were evaporated to dryness and the residue dried at  $100^{\circ}$  C.

Crucible with the residue	= 24.891 grams.
Crucible alone	= 24.350 "
Residue	= 0.541 "

0.541 grams of residue is contained in 10 cc. of urine, so that in 1,000 cc. of urine there are 54.1 grams.

II. 1,000 cc. of urine of 1.024 sp. gr. = 1024.0 grams.

Of this the residue = 54.1 “

Evaporated water = 969.9 “

2. Even when carried out with the greatest care, this method described under 1 gives inaccurate results, since during the evaporation and drying the acid phosphate of sodium has a destructive action on the urea and decomposes it partially into carbonic acid and ammonia. The latter combines with the acid phosphate of sodium to form ammonio-sodic phosphate, a compound which is again decomposed at 100° C. with the evolution of ammonia. As long as the evaporation and drying is continued, therefore, an uninterrupted evolution of ammonia is observed, which proceeds from the decomposed urea, while the residue always retains its acid reaction. If the evaporation and drying is carried on in an apparatus in which the ammonia

FIG. 17.

which is set free can be collected and estimated, a satisfactory result is at once obtained, if the ammonia is reckoned as urea, from the decomposition of which it has without doubt arisen, and this amount is added to the residue found on weigh-

ing. Very satisfactory results may be obtained with the apparatus (fig. 17) constructed by me, which allows of the collection and estimation of the disengaged ammonia.

A is a water bath twelve centimeters high and eleven centimeters broad, with a tin tube of two and a half or three centimeters in diameter passing through its centre. A glass tube, BB, of the shape represented in the figure, can be readily pushed through this tin tube, and the porcelain dish seven or eight centimeters long and one and  $\frac{1}{8}$  broad, for holding the urine, is placed inside. The glass tube, BB, is connected at one end with the chloride of calcium tube, F, by means of a cork, while the portion drawn out and bent is connected by means of a doubly perforated cork with the little flask D, in which standard sulphuric acid is placed. The drawn-out arm of the tube BB reaches nearly to the bottom of the flask. The flask D is connected with the aspirator E through the second perforation of the cork.

The estimation is now readily made. The porcelain dish is first about three-quarters filled with not too small glass splinters, it is dried at 100° C., and then accurately weighed in a glass tube which can be closed with a cork covered with tin foil. Then exactly two cc. of urine are allowed to run from a pipette, which best holds just this amount, on to the pieces of glass in the porcelain dish, and it is carefully pushed into the tube BB, which is already connected with the little flask D, in which there are ten cc. of standard sulphuric acid, and the latter is connected with the aspirator. Then the glass tube is carefully pushed through the tin tube of the water bath, and the second opening is closed with the chloride of calcium tube F, by holding the glass tube firmly with the left hand and tightly securing the cork in with the right. When the water in A is heated to boiling, the cock of the aspirator is opened, having first found that the apparatus is air-tight, and the water allowed to flow out in such quantity that the air dried in F shall pass through the sulphuric acid in D in bubbles which follow each other every second. The urine is evaporated in this manner at 100° C. in a stream of dry air. In three-quarters of an hour this operation is finished, but the residue of the urine persistently retains the water, and must, therefore, be kept at the same temperature for some time longer. If illuminating gas is at the

disposal of the experimenter, a stream of dry gas may suitably replace the stream of air, and may finally be conducted to the lamp under A and burned. The aspirator is thus rendered superfluous. The pieces of glass facilitate exsiccation very much, so that in about three hours the entire operation may be regarded as completed. The gas or air stream is now interrupted, the chloride of calcium tube removed, the tube removed from the water bath, and the little porcelain dish introduced into the tube in which it was weighed before the evaporation, which tube is then immediately tightly closed with the cork. After complete cooling in the desiccator the tube is weighed; the increase of weight gives the amount of urinary residue found in two cc. of urine. Next the ammonia evolved must be estimated. First the carbonate of ammonium which is usually found sublimed in the evaporating tube is washed into the flask, then the cork is removed, and the bent arm is also washed with water from a wash bottle, one or two drops of tincture of litmus or cyanine solution are added, the fluid is heated to boiling to drive out all carbonic acid, and the unsaturated acid titrated with sodic hydrate. It is well to calculate the sodic hydrate immediately as urea; the number of cc. now used, less than the number required to saturate the original acid, directly gives the amount of urea decomposed, which added to the weighed residue yields the whole amount of solid constituents of the urine.

The standard sulphuric acid used in this estimation should contain 2.667 grams of sulphuric acid in the liter, so that 1 cc. of it shall be saturated by 0.0011335 grams of ammonia, corresponding to 0.002 gram of urea. If, then, to such sulphuric acid sodic hydrate is added of such a strength that 1 cc. of the former requires just 2 cc. of the latter for its exact saturation, each cc. of the sodic hydrate, less than 20, required to saturate the 10 cc. of sulphuric acid, exactly corresponds to 1 milligram of urea.

#### Example:

Two cc. of urine yielded 0.10 grams of solid residue in the little dish. The ten cc. of sulphuric acid required sixteen cc. of sodic hydrate after the experiment was ended; there were, therefore, four cc. neutralized by the ammonia evolved, and these correspond to

0.004 grams of urea. Two cc. of urine then contained 0.104 grams of residue, and one thousand parts 52.0 grams.

3. The whole amount of the solid constituents of the urine can be approximately reckoned from the specific gravity when determined with accuracy and with exact observation of the temperature. This is a fact which I have convinced myself of by a series of determinations. (See Analytical Experiments.) If the three last figures of the specific gravity carried out to four decimals is multiplied by the number 0.233, the product gives approximately the amount of solid matters in 1,000 cc. of urine.

Example:

The amount of urine in twenty-four hours = 1.500 cc.

The specific gravity                      "                      "                      = 1.0134

The amount of solid matters in 1,000 cc. =  $(0.233 \times 134) = 31.22$  grams. The amount in 1,500 cc. therefore = 46.83 grams, while by weighing, according to method 2, 46.59 were found.

The table given in the analytical appendix shows how large the error may be in this method.

## § 60. ESTIMATION OF THE NON-VOLATILE SALTS.

To determine the total non-volatile salts contained in the urine, a measured quantity of urine is evaporated to dryness and ignited until all of the carbon is consumed. Yet this simple method is subject to several sources of error, for at too high a temperature some of the chlorides present volatilize, and at a red heat the separated carbon may reduce the sulphates and phosphates, changing the former into sulphides and developing phosphorus fumes from the latter. Besides, complete ignition of the charcoal requires a long time, since enclosed by the large amount of chlorides which are readily fusible, it is protected from contact with the air. All of the above sources of error may be reduced to a minimum by the following method when carried out with care.

Ten cc. of urine first filtered are placed in a small weighed platinum dish with a well-fitting cover and evaporated to dryness on the water bath. The dish is then placed on a platinum

triangle and carefully heated with as little fire as possible until the organic matters are carbonized, and no more gas is evolved from the swollen mass. After cooling, the contents of the dish are covered with boiling water, it is allowed to stand a short time, and the colorless feebly alkaline fluid is filtered through the smallest possible filter, the weight of whose ash is known. The carbonized residue is freed from all soluble salts by repeatedly washing it with hot water, the filter is then washed and finally dried in the same platinum dish on a water bath. The platinum dish and its contents are then heated to a low red heat, and the carbonized residue and the filter are thus easily and completely consumed. The platinum dish, when the residue is free from all carbon, is put back on the water bath, the fluid obtained by extracting the first carbon residue is added and evaporated to dryness. The salts obtained are last of all heated to a low red heat before weighing, but the saline residue must first be dried a long time, since otherwise a loss may readily occur by decrepitation. For the same reason the dish must be kept well covered during the ignition and the temperature only raised to a dull red in order that no chlorides shall volatilize.

If the dish is finally cooled over sulphuric acid, weighed, and the weight of the dish and filter ash subtracted from the gross weight, the remainder is the total amount of the non-volatile salts contained in ten cc. of urine.

Example :

The amount of urine = 1,500 cc.	
The platinum dish with cover and ash of 10 cc.	= 14·243 grams.
The platinum dish alone	= 14·120   “
	<hr/>
	0·123   “
Filter ash	= 0·001
	<hr/>
Non-volatile salts in 10 cc. of urine = 0·122	
10 : 0·122 = 1,500 : $x$ . $x$ = 18·3 grams.	

## § 61. ESTIMATION OF THE COLORING MATTERS.

A. *The Color Table.* (See Plate IV.)

Vogel has succeeded by a large number of observations in establishing the color scales, given below, for the different

shades of healthy and pathological urine. These he has imitated artificially by mixing different amounts of gamboge, carmine lake, and Prussian blue. He distinguishes three groups or shades.

*I. Group. Yellow Urines.*

The color is a yellow (gamboge) more or less diluted with water. The group has three shades of color whose starting point is the rarely occurring colorless urine.

1. Pale yellow (gamboge with much water).
2. Light yellow (gamboge with little water).
3. Yellow (gamboge with very little water).

*II. Group. Reddish Urines.*

Red is more or less mingled with yellow (gamboge with carmine lake). The urines of this group are designated by the adjective "high-colored." Three shades of color belong here also:

4. Reddish yellow. A little red is mingled with the yellow, but the latter is more prominent. (Gamboge with a little carmine lake.)

5. Yellowish red. The red color together with the yellow is more distinct. (Gamboge with a little more carmine lake.)

6. Red. The red predominates, yet there is still some yellow mixed with it. (Carmine lake with a little gamboge.)

*III. Group. Brown (dark) Urines.*

The red color passes through brown almost into black. (Gamboge and carmine lake with more or less Prussian blue.)

7. Brown red. A little brown is mingled with the red.

8. Red brown. More brown than the above.

9. Brownish black. Almost black, yet with a tinge of brownish red.

The practised eye can still distinguish intermediate shades between these, when it can be said: the color is between light yellow and yellow; it approaches nearer to the reddish yellow than the yellowish red, etc., but according to Vogel these nine shades suffice.

B. *Value of these Color Scales.* The shades of color correspond to certain relative amounts of coloring matter. It has been



found that by diluting a higher number with water all the lower numbers can be produced. All nine shades of color are in the same series, so that the color of urines may be regarded as different dilutions of one and the same coloring matter. But we must naturally leave out of question the accidental colors, which rarely occur, due to the presence of bile, medicinal or food pigments, etc. These experiments carried out quantitatively prove that a urine diluted with an equal volume of water produces nearly the next lower shade : 200 cc. of urine of a yellowish-red color diluted with 200 cc. of water becomes reddish yellow, and so forth. These relations are about the same for all parts of the scale, from which it follows that they may serve to determine the relative amount of coloring matter in different urines.

The following table serves for such quantitative estimations :

I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	
1	2	4	8	16	32	64	128	256	pale yellow = I.
	1	2	4	8	16	32	64	128	light yellow = II.
		1	2	4	8	16	32	64	yellow = III.
			1	2	4	8	16	32	reddish yellow = IV.
				1	2	4	8	16	yellowish red = V.
					1	2	4	8	red = VI.
						1	2	4	brownish red = VII.
							1	2	reddish brown = VIII.
								1	brownish black = IX.

C. *Application of the Method.* This table which has been drawn up serves us for the quantitative comparison of the amounts of urinary coloring matter eliminated; it shows how much coloring matter equal parts of urine of different colors contain relatively. If a certain volume of pale-yellow urine contains one part of coloring matter, the same volume of yellowish red contains sixteen parts, of red thirty-two parts, of brownish black two hundred and fifty-six parts, etc. It further shows that one volume of yellow urine contains just as much coloring matter as four volumes of pale yellow, one volume of red as much as four volumes of reddish yellow, or thirty-two volumes of pale yellow, etc. If, therefore, one person passes 1,000 cc. of yellow urine in twenty-four hours, and another in the same time 4,000 cc. of pale yellow, both secrete an equal amount of coloring matter.

Now, in order to make an approximate comparison by figures

possible, Vogel places the quantity of coloring matter which 1,000 cc. of pale yellow urine contains = 1.

But in order to obtain harmonious results by comparing the color of the urine with the color table, the urine must in the first place be perfectly clear; in most cases, therefore, it must be filtered, and in the second place it must be examined by transmitted light in a layer four or five inches thick. Therefore, glasses four or five inches in diameter are used which can hold 800 or 1,000 cc., since the color in thinner layers will appear too light when compared with the table.

Example:

1,800 cc. of urine having a yellow color are passed.

1,000 cc. pale yellow = 1 part coloring matter; but yellow, according to the table, contains four times as much; therefore, we have the following proportion:

$1,000 : 4 = 1,800 : x = 7.2$  as the amount of coloring matter in 1,800 cc. of yellow urine, the coloring matter in 1,000 cc. of pale yellow urine being considered as the unit.

## QUANTITATIVE ESTIMATIONS OF INDIVIDUAL SUBSTANCES.

### § 62. VOLUMETRIC ANALYSIS.

The use of this method renders urinary analysis simpler and its performance more rapid. In determining the weight of a body by titration, we do not do it by weighing the compound precipitated by any reagent, but we ascertain the amount of the solution of a reagent necessary to complete a certain reaction, and from this reckon the quantity of the material which was present. These determinations, which are always carried out by measuring the solution of the reagent used, are successful, however, only under certain conditions, on which alone their accuracy depends; these are the following:

1. The strength of the solution of the reagent must be most accurately known, and the amount of the standard solutions used must be capable of exact determination.

2. The end of the reaction, that is, the point at which just enough of the standard solution has been added, must be recognized in a distinct and striking manner.

3. The decomposition, on the accomplishment of which the analysis depends, must always remain the same.

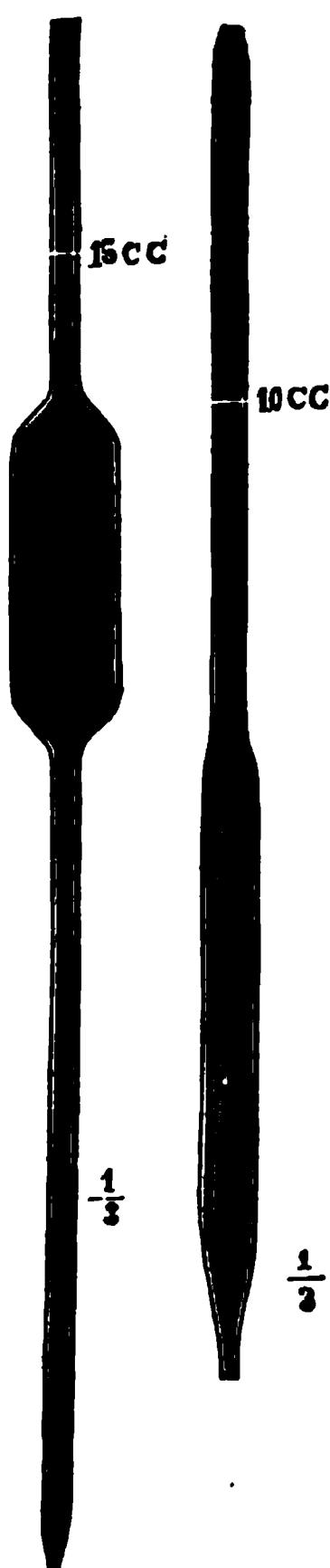
4. The decomposition must be so managed that none of the active or reactive agent is lost.

General rules for attaining these conditions cannot be given well, since they differ with each substance, and must be treated more in detail in speaking of each one separately. Yet, before I pass to the individual methods, it is necessary to speak of the apparatus required, as well as generalities in their execution.

### § 63. I. APPARATUS.

On account of the superiority of the French system of weights

FIG. 18.



and measures, these only are employed in quantitative chemical determinations. It is well known that there is here an intimate connection between volume and weight, so that 1,000 cc. of water at its greatest density, that is, at  $+4^{\circ}\text{C.}$ , = 1 liter, which weighs exactly one kilogram or 1,000 grams; a cubic centimeter, therefore, corresponds exactly to one gram.

The measuring vessels in which volumetric analyses are performed are all divided into cubic centimeters (cc.); of these may be mentioned:

1. *The Graduated Pipette.* This is the glass apparatus whose form is shown in fig. 18, *a* and *b*; it is used in measuring off the necessary fluids, and, therefore, has a mark on its neck up to which it contains just 50, 20, 15, 10, 4, 3, and 2 cc. In measuring, the end of the pipette is dipped into the fluid, which is sucked up until it has risen above the mark in the neck; the opening above is then closed by the finger slightly moistened (neither wholly dry nor yet wet), the pipette is freed from fluid adhering to the outside by wiping, and the solution is allowed to flow from the pipette by slightly lifting the finger, until it stands exactly at a level with the mark; this point is determined by holding the surface of the fluid on a level with the eye.

Having reached this point the pipette is tightly closed with the

finger again, and the contents may be allowed to flow into any vessel at pleasure. It must be observed, however, how the pipette has been graduated, whether the last drop, which collects at the lower end after a time and which may be removed by blowing it out, must be taken or not. The most accurate and most suitable are the "pipettes à l'écoulement," which are so graduated that they allow the designated amount of fluid to flow out directly in a stream, so that the drop which remains adherent to the lower end need not be blown out. It is pre-

ferable in all cases to place the point of the pipette on the moistened side of the glass, while it is being emptied. This method of measuring gives the most constant results; it is self-evident, however, that the pipettes must be graduated according to this method of reading off. For urinary analysis pipettes of 50, 30, 20, 15, 10, 3, and 2 cc. are necessary for a complete outfit.

FIG. 20.

The following apparatus serves for measuring standard solutions.

## 2. Mohr's Pipette.

These pipettes are graduated throughout their entire length, and hold 30 or 40 cc., each of which is again divided into ten parts (that is, into  $\frac{1}{10}$  cc.). (Fig. 19.) They are not drawn out at the top, so that fluids may be easily

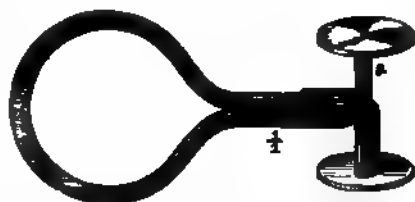


FIG. 21.

poured into them, and the opening may then be closed with a cork. The following very simple contrivance, and one which at the same time answers all requirements, allows the standard

solutions to flow out drop by drop. A short piece of vulcanized rubber tubing, fig. 20, *aa*, which is pressed together by a wire clamp *bb*, fig. 21, by which it is hermetically closed, but can be more or less opened by pressure applied to the two plates *c, c*, has a small glass tube, *d*, ending in a fine point, introduced into its lower end. This rubber tube is drawn over the small end, *b*, of the pipette, represented in fig. 19, which is then fastened in a wooden stand so that it is perfectly vertical. Fig. 22 shows the entire apparatus. When ready for use the pipette is filled to the 0-point with the standard solution, the urine to be tested is measured off, and the standard solution is allowed to flow, at last drop by drop, by opening the wire clamp until the right point is exactly reached. By means of this ingenious contrivance we not only obtain a

FIG. 23.

FIG. 21.

more rapid flow, but also a surer discharge of the single drops. In a series of investigations which extend over a long time it is well to have two or more such pipettes on a stand, so that

they may be left standing wholly or partly filled, if the upper opening is closed with a stopper, without danger of evaporation.

Fig. 23 shows a similar arrangement which might be very useful to physicians, and is sufficiently intelligible without an explanation. *ab*, on which the eight arms are fastened, is a brass case which rests on a clamp, and which can be readily turned on its axis. The pipettes are held above by a screw clamp, while below they simply rest on the holder, which is turned out conically and has a hinge, so that the pipettes can be readily taken out. *c, c, c* are pieces of cardboard which are fastened by a small clamp to each arm, and on which the nature of the fluid in the pipette is recorded. Finally, *d* is a level resting on four screws to keep the whole apparatus perpendicular. It is self-evident that by constructing the apparatus somewhat larger six or eight pipettes may be held by it.

The same purpose is served by

3. *The Graduated Burette.* The ordinary form of this ingenious apparatus is pictured in fig. 24. The narrow tube serves for pouring the fluid out, and must, therefore, be placed somewhat lower than the opening of the broad tube, so that the fluid can be conveniently removed. These burettes either hold 30 cc. and are then divided into tenths like the pipettes in fig. 19, or they contain 50 cc. and are then divided into 100 degrees, each one of which marks half a cc. When used they are filled to above the 0-point with the standard solution, and then the excess is poured out of the narrow tube exactly to the 0. Mohr's apparatus described above renders these easily perishable instruments rather superfluous. The Mohr pipette and the burette must each be graduated *à l'écoulement*.

4. *The Graduated Cylinder.* This is used for preparing the standard solutions, and is represented in fig. 25. Such a cylinder must contain 500 or 600 cc. and have a division line for every 5 cc. The so-called measuring flasks serve the same purpose, fig. 26; they are filled to a mark in the neck, and hold exactly one, one-half, or one-quarter of a liter. These

FIG. 24.

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10

20

30

40

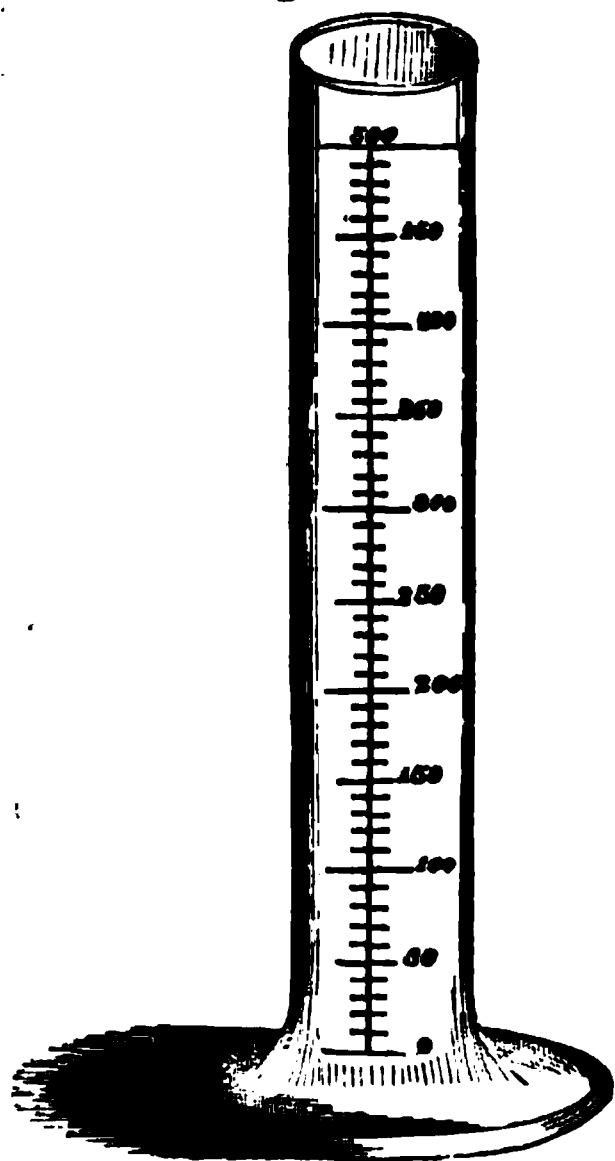
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flasks are preferable to the cylinder in the preparation of standard solutions.\*

## § 64. II. PERFORMANCE.

In carrying out the volumetric method, as already remarked above, we must pay the greatest attention to the necessary standard solutions, since the correctness of the results obtained depends solely on the accuracy of these. Special directions will be given with each method, and we must remark at the same time, that such normal solutions must always be only prepared and used at medium temperatures, since their volume would be considerably changed by heat. Furthermore, certain

Fig. 25.



precautions are to be observed in reading off the level of the fluid in the graduates, which precautions must be accurately followed in carrying out the methods:

1. Care must be taken that no bubbles render the height of the fluid uncertain; they must, therefore, be removed either by waiting or by being broken up by a glass rod.

2. The surface of the fluid must be level; this is attained in pipettes by allowing them to hang freely, but in burettes best when they are placed against a window pane.

3. If any sort of fluid is poured into a narrow tube, it is observed that its surface forms a curve as the result of capillarity; if this curve is carefully examined, best by transmitted light,

Fig. 26.




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\* The mechanician Niemann, in Alfeld near Hanover, Germany, furnishes the above pieces of apparatus of great excellence and at low prices.

several zones may be readily distinguished in it (Fig. 27.) Now in reading off it is not immaterial whether sometimes the upper and sometimes the lower edge or the middle of the curve coincides with the division line of the tube. The measurements are made most accurately when the eye is placed on a level with the lower edge of the dark zone, fig. 27, after the pipette or burette has been brought to the perpendicular, and the division line of the tube is read off from this; Fig. 27. this edge can be most sharply brought out and observed by transmitted light.

If the urine to be tested has been measured in this manner, and the pipette or burette has been filled with the standard solution, the latter is allowed to flow into the urine drop by drop until the end reaction distinctly appears. If this end reaction is very apparent through the whole fluid, it shows a great excellence of the method; but if this is not the case, the mixture must be frequently tested toward the end of the experiment until the right point has been finally reached. Each method, moreover, has its own reaction, which must be spoken of separately. If the standard solution has been added up to this point, the volume used is read off with the observance of the above precautions, and the amount of the substance to be determined is reckoned from it.

For example: If, in estimating the amount of urea in 10 cc. of urine, 20 cc. of the mercury solution have been used, each cc. of which exactly corresponds to 10 milligrams of urea, there are consequently in those 10 cc. of urine ( $20 \times 10$ ) 200 milligrams of urea; in 1,000 cc. then 20.00 grams.

Lastly, we must observe, in using a burette (fig. 24) care must be taken not to spill the fluid out of the wide tube, by inclining it too much. This may readily happen, if a drop remains hanging in the narrow delivery tube and hinders the penetration of the column of fluid; this disturbing element, however, may be easily removed by blowing into the tube.

The amount of urea, chlorine, phosphoric acid, free acids, sulphuric acid, lime, ammonia, and sugar in the urine may be determined volumetrically.



## § 65. ESTIMATION OF UREA BY LIEBIG'S METHOD.

*A. Principle.* If a dilute solution of mercuric nitrate is added to a dilute solution of urea, and if the free acid of the mixture is neutralized from time to time with carbonate of sodium, a flocculent, bulky, white precipitate is obtained, which is insoluble in water. If the solution of mercury and carbonate of sodium are added alternately as long as this precipitate is formed, a point occurs at which the mixture assumes a yellow color, due to the formation of mercuric hydrate or a basic salt from the addition of the carbonate of sodium. If now the fluid is filtered, it contains no determinable amount of urea; all of the urea is precipitated in combination with mercuric oxide. The precipitate which takes place contains to one equivalent of urea four equivalents of mercuric oxide. The above-mentioned yellow color with carbonate of sodium will not begin until a volume of the mercuric solution, in which there are seventy-seven parts of oxide, has been added to ten parts of urea in the solution of urea, that is, four equivalents to one equivalent of urea.

If no more mercuric solution is added to the solution of urea than is necessary for a complete precipitation, the mixture tested with carbonate of sodium still remains white; but if it is now allowed to stand a few hours the character of the precipitate changes, it becomes crystalline, and the supernatant fluid then gives a yellow precipitate with alkalies. In the acid solution on long standing the compound with four equivalents of mercuric oxide is reduced to a compound which contains a less amount, that is, a part of the mercuric oxide enters into solution again.

In order now to reach the point at which all of the urea is precipitated, and to determine whether the necessary amount of the mercuric solution has been added to form the compound with four equivalents of mercuric oxide, it is necessary to neutralize with carbonate of sodium. If a drop of the mixture added to a drop of a solution of carbonate of sodium in a watch glass remains white, free urea is still present in the fluid: if, when the two drops flow together, a yellow pellicle appears on the surface, the limit is reached, or, more accurately, is a little exceeded. To bring out this end reaction, only a very slight excess of mercuric oxide is necessary.

If we know the amount of oxide which our mercuric solution contains, and if we further determine the volume which must be added to a solution of urea of unknown strength until the latter is completely precipitated (until on neutralizing a drop of the mixture with carbonate of sodium a yellow color appears), the amount of urea in the solution can be reckoned. Or, on the other hand, if a certain volume of the mercury solution has been required to precipitate a known amount of urea, for example, 100 mgrm., the same volume of the mercury solution will indicate the same amount of urea, 100 mgrm., in solutions containing unknown amounts.

*B. Preparation of the Necessary Solutions.*

1. *Urea Solution of Known Strength.* Four grams of pure urea, dried at  $100^{\circ}$  C., are dissolved in water and diluted until the volume of fluid amounts to exactly 200 cc. 10 cc. of this solution contain exactly 200 mgrm. of urea.

2. *Solution of Mercuric Nitrate.* The solution of mercury which serves to determine the urea in urine must be of such a strength that 20 cc. of it just suffice to completely precipitate the urea in 10 cc. of solution 1 (in which there are 200 mgrm. of urea).

1 cc. of the mercury solution should correspond to 10 mgrm. of urea, and for this purpose it must in the first place contain a quantity of oxide sufficient to form with 200 mgrm. of urea the compound with four equivalents of mercuric oxide, and also a slight excess which serves to indicate the complete precipitation of the urea, so that after adding the last drop of the 20 cc. to 10 cc. of the solution of urea a distinct yellow color is evident, when a few drops of the mixture are treated with carbonate of sodium on a watch glass.

Liebig has found that to 100 mgrm. of urea, which according to the calculation require 720 mgrm. of mercuric oxide, 10 cc. of the mercury solution must contain 772 mgrm. of oxide to produce in dilute fluids the reaction of mercuric oxide with carbonate of sodium distinctly. Each cc. of the solution must, therefore, contain an excess of 5.2 mgrm. of mercuric oxide; and a liter 77.2 gm. of oxide in all, or 71.48 gm. of metallic mercury.

*a. Preparation from Pure Mercury.*

71.48 gm. of chemically pure mercury are weighed off, placed in a beaker and dissolved in pure nitric acid. When solution

has resulted, it is warmed and nitric acid frequently added until no more traces of nitrous vapors are seen to escape, in other words, until the mercurous oxide is completely transformed into mercuric oxide, and it is then evaporated in the same vessel to a thick syrup. The mercuric nitrate thus obtained is then diluted with water to exactly a liter; if a basic salt separates, it is allowed to settle, the clear fluid is carefully poured off, and the precipitate is dissolved again by a few drops of nitric acid. The accuracy of the solution thus obtained must now be tested in the manner described below.

*b. Preparation from Mercuric Oxide.*

It is best to prepare the mercury solution from pure mercuric oxide; it can also be readily prepared in a porcelain dish by heating mercurous nitrate, which has been recrystallized several times. There occurs in commerce a mercuric oxide sufficiently pure for this purpose, for when it leaves no visible residue when heated on platinum foil, it is quite suitable. 77.2 gm. of such mercuric oxide which has been dried at 100° C. are accurately weighed, dissolved in as little nitric acid as possible in a porcelain dish at a gentle heat, evaporated to a syrupy consistency and then diluted to one liter. If a basic salt should separate, nitric acid is added drop by drop until the precipitate just disappears.

According to Dragendorff, yellow mercuric oxide is precipitated from a solution of 96.855 gm. of pure corrosive sublimate by dilute sodic hydrate; it is first washed by decantation and then on a filter. This precipitate is afterward dissolved in a sufficient amount of nitric acid and diluted to nearly a liter. The exact strength of the solution is fixed by titrating with the normal solution of urea as given under d.

*c. Preparation from Mercurous Nitrate.*

If no chemically pure mercury or mercuric oxide can be obtained, crystalline mercurous nitrate must be procured, and this converted into mercuric oxide by heating with nitric acid.

*d. To Standardize the Prepared Mercury Solution.*

Exactly 10 cc. of the solution of urea, 1, are measured off with a pipette, poured into a small beaker, and then the approximately dilute mercury solution is added drop by drop, until a few drops of the mixture neutralized with carbonate of sodium on a watch glass give a distinct yellow color.

If, for example, 19.25 cc. of the mercury solution have been required to produce the end reaction, 7.5 cc. of water are added to each 192.5 cc., and thus 200 cc. of solution are obtained, of which 20 cc. will exactly precipitate the urea from 10 cc. of the urea solution. Its accuracy is confirmed by a second test: if the yellow color appears distinctly after adding 20 cc., the solution may be used for determining the urea in urine.

3. *Baryta Solution.* This is obtained by mixing one volume of nitrate of barium solution and two volumes of caustic baryta, both solutions saturated in the cold.

C. *Performance.*

In order to be able to determine the urea in the urine by this method, the phosphoric acid must first be removed. Therefore 40 cc. of urine are measured off, with a pipette, treated with 20 cc. of the baryta solution, and the precipitate which occurs is separated by filtering through a dry filter. For each analysis 15 cc. of the filtrate are measured off, which, therefore, contain exactly 10 cc. of urine. In most cases one volume of the baryta solution to two volumes of urine is sufficient to remove all of the phosphoric and sulphuric acids, so that some baryta still remains in the solution. But if the urine contains alkaline carbonates, which under certain circumstances may consist of carbonate of ammonium from the decomposed urea, or if it has a very strongly acid reaction, one volume of baryta solution to two volumes of urine are often not sufficient; then more must be taken. If three volumes of baryta solution are mixed with four volumes of urine, 17.5 cc. of the filtrate are taken (corresponding to 10 cc. of urine); with equal volumes of baryta solution and urine 20 cc. are taken for the analysis, etc.

The standard mercury solution is allowed to flow from a Mohr pipette into this measured amount of urine without previously neutralizing and with constant stirring, and when no more precipitation is observed and the mixture no longer thickens, the test is performed. For this purpose a few drops of the mixture are placed on a watch glass by means of a glass rod, and a few drops of carbonate of sodium solution are allowed to flow on to it from the edge of the watch glass; a Mohr's india-rubber pipette is good for this purpose. If the mixture retains its white color after some seconds, there is still some free urea present, and a few more drops of the mercury solution are added and it is

again tested; this process is repeated until at a new trial on the watch glass a distinct yellow color results after the carbonate of sodium solution has been added. The shade must naturally be the same as that at which the mercury solution was originally standardized, for by sometimes adding the solution until a weak and sometimes until a strong yellow color is produced, an error is caused, which with a little experience can be avoided.

The amount of urea is then reckoned from the number of cc. of the mercury solution which have been used, but under certain circumstances a few corrections are to be made which are mentioned below.

*D. Modification of the Process and Corrections Required by Different Circumstances.*

*1. The Urine contains more than 2 per cent. of Urea.*

Our mercury solution is standardized by a urea solution which contained 2 per cent. of urea; we need, therefore, for the complete precipitation of the urea in 15 cc. of our urea solution, and for producing the end reaction with carbonate of sodium, 30 cc. of mercury solution. The mixture, therefore, will amount to 45 cc., and we have in it  $30 \times 5.2 = 156$  mgrm. of free mercuric oxide; each cc. contains, therefore, 3.47 mgrm. If the 15 cc. of the urea solution contain 4 per cent. of urea, and if to 15 cc. of the same 60 cc. of mercury solution are added, there are together 75 cc. of mixture, in which there are  $60 \times 5.2 = 312$  mgrm. of free mercuric oxide, in each cc., therefore, 4.16 mgrm., and consequently 0.69 mgrm. more oxide than is necessary to produce the end reaction with carbonate of sodium.

It has thus happened that in a urinary analysis an error is made when the amount of urea is more than 2 per cent., so that the true amount of urea is diminished. If the urine contains, as in the above case, 4 per cent. of urea, 60 cc. of the mercury solution would not be necessary, but only 59.37 cc.

This error is avoided by adding, when 15 cc. of urine are taken, for the number of cc. of mercury solution more than 30 cc. which are used, half this number of cc. of water to the mixture before testing with carbonate of sodium. If, for example, 50 cc. of mercuric solution are used to 15 cc. of urine, that is, 20 cc. more than 30, then 10 cc. of water must be added before testing with carbonate of sodium.

2. *The Urine contains less than 2 per cent of Urea.*

For the same reasons which are given above, when the urea in the urine only amounts to 1 per cent., to obtain the end reaction there will be required for 15 cc. of urine, not 15 cc. of the mercury solution, but 15.3 cc. Through this error the amount of urea is found to be increased, and in order to obviate it when the urine is dilute, for every 5 cc. of the mercury solution less than 30 cc. which are used, 0.1 cc. must be subtracted from the number of the cc. of mercury solution used. If to 15 cc. of urine 25 cc. of mercury solution are used, that is, 5 less than 30 cc., for these 5 cc. 0.1 cc. is subtracted and the calculation made for only 24.9 cc. of the mercury solution.

3. *The Urine contains Chloride of Sodium.*

When the amount of chloride of sodium reaches 1 or 1½ per cent., it exercises an influence on the determination of urea with mercuric nitrate. If, for instance, to 10 cc. of our urea solution are added 20 cc. of the mercuric solution, a distinct reaction for mercury with carbonate of sodium is obtained at the end, but this reaction fails when we add 100 to 200 mgrms. of chloride of sodium to the solution of urea, and in order to make it appear now we must add 1½ or 2½ cc. more of the mercury solution. The determination of the urea comes out 15 or 25 mgrm. too high, therefore. The same is the case with the urine also if it contains 1 or 1½ per cent. of chloride of sodium. The formation of corrosive sublimate is the cause of this.

Mercuric nitrate and chloride of sodium mutually decompose each other, as is well known, into corrosive sublimate and nitrate of sodium, but corrosive sublimate does not precipitate a feebly acid solution of urea, and therefore remains in solution. This is naturally the case also in the determination of urea in the urine; the excess of mercuric oxide which should give the yellow color on the addition of carbonate of sodium is not now, however, in the form of a nitrate, but of corrosive sublimate together with free nitric acid. If we now add carbonate of sodium to this mixture bicarbonate of sodium is formed by the free nitric acid, and this does not precipitate the corrosive sublimate, therefore the reaction does not occur, and we must add some more mercuric nitrate in order to obtain it. If the mixture contains a larger amount of chloride of sodium than 1 or 1½ per cent., the amount of corrosive sublimate formed increases with

it, but by the addition of carbonate of sodium the carbonic acid which is freed is no longer sufficient to prevent the precipitation of the mercuric oxide; there results, therefore, now a brownish-yellow precipitate. According to Liebig this is the reason why the indication of the complete precipitation of urea in the presence of a certain quantity of chloride of sodium (1 or  $1\frac{1}{2}$  per cent.) is deferred, and the limit of the reaction does not extend, if the amount of chloride of sodium increases still more.

If a urine, therefore, contains from 1 to  $1\frac{1}{2}$  per cent. of chloride of sodium, to obtain the right number of milligrams of urea in 10 cc. of urine two must be subtracted from the whole number of cc. of the mercury solution used, and the remainder only reckoned for urea; the results obtained are then more accurate and comparable.

If it is necessary to know the absolute quantity of urea in the urine, the chlorine must first be removed by a solution of nitrate of silver, 1 cc. of which exactly corresponds to 10 mgrm. of chloride of sodium.

This solution of silver is obtained by dissolving 29.075 grm. of fused nitrate of silver in water and diluting the solution to a liter. 1 cc. corresponds to 10 mgrm. of chloride of sodium; it is the same silver solution which is used for determining the chlorine according to Mohr's method, § 66, B, 1. The method of performing it is as follows:

The amount of chloride of sodium in 10 cc. of the original urine is determined by means of the silver solution according to § 66. If, for example, we have used 17.5 cc., the presence of 175 mgrm. of chloride of sodium is indicated. We now measure off with a pipette 30 cc. of the mixture of baryta and urine, render the reaction feebly though distinctly acid by a few drops of nitric acid and treat this with  $2 \times 17.5$  cc. = 35 cc. of the silver solution. The whole volume of the mixture amounts to 65 cc.; the precipitated chloride of silver is filtered off and half the mixed fluid, that is, 32.5 cc., in which there are 10 cc. of urine, is taken from the filtrate.

The urea is now determined in this amount as is usual by the standard solution of mercury, in which, however, the dilution resulting from the addition of the silver solution must be taken into account. (D, 2.)

If the 32.5 cc. of the urine mixture taken for the titration of



the urea contained 2 per cent. of urea, 65 cc. of the mercury solution would be required. But if only 25 cc. were required, then according to D, 2, for  $(65 - 25)$  40 cc. 0.8 cc. must be subtracted. Accordingly the urea must be calculated for only 24.2 cc.

*Rautenberg's Method.\** Two specimens of 15 cc. each of the urine mixture are measured off. One is feebly acidulated with nitric acid, and the mercury solution, which serves for determining the urea, is allowed to flow into it until a permanent cloudiness appears. The number of cc. of the mercury solution used up to this point forms the correction for the chloride of sodium, and is taken into account in subtraction. (See § 13, C, 3.) The second specimen is used for precipitating the urea. The mercury solution is allowed to gradually flow in without previously acidifying, and the mixture is kept neutral by successive additions of pure precipitated calcic carbonate. In order to determine whether all of the urea is precipitated, a large drop of the mixture is placed by means of a glass rod on a clean glass plate covered thickly on its under side with asphaltum varnish, and it is covered with a drop of bicarbonate of sodium stirred up with water; the appearance of the first distinct traces of a yellow color indicates the end of the reaction. By using the bicarbonate of sodium the disturbing influence of the corrosive sublimate which is formed is entirely obviated, so that the urine can be accurately titrated up to one or two mgrm. of urea. The bicarbonate, however, must contain no normal carbonate, and must, therefore, before using be washed with small amounts of water after being rubbed up finely, until it no longer browns turmeric paper.

#### 4. *The Urine contains Albumen.*

If the urine contains albumen, the urea cannot be directly determined by the method given, but the albumen must first be removed. The usual procedure, therefore, suffers the following modification:

100 to 200 cc. of urine are heated in a closed vessel on a water bath, until a complete coagulation of the albumen has taken place and thick flocculi have separated, so that the urine appears clear. If the coarse flocculent precipitate does

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\* *Annalen d. Chem. u. Pharm.*, Band 183, p. 55.



not form from lack of free acid, acetic acid is carefully added drop by drop to the hot fluid until it has taken place. Heating for half an hour is amply sufficient. Then after the fluid containing the coagulated albumen has become cold, it is filtered and the clear filtrate is used to estimate the urea, phosphoric acid, etc.

5. *The Urine contains Carbonate of Ammonium.*

Since the carbonate of ammonium in urine comes from decomposed urea, it may be of interest under certain circumstances to estimate the amount of urea, which corresponds to the carbonate of ammonium. Liebig found that foul ammoniacal urine, when decomposition had not gone too far, frequently gave the same results as fresh urine. If in such a urine a precipitate which contains two equivalents of mercuric oxide to one equivalent of ammonia occurs after the addition of mercuric nitrate, an equal amount of mercuric oxide is required for decomposed as well as for undecomposed urea, since the latter in its decomposition yields two equivalents of ammonia. (One equivalent of urea to four equivalents of mercuric oxide.) Investigations which were undertaken, however, showed that this relation did not remain constant, and that frequently more of the mercury solution was required. If, therefore, we wish for accurate results, the ammonia and urea must be determined separately, and the former must be recalculated for urea. There are two ways to do this:

a. One portion of the urine is precipitated with the baryta solution, a volume of the mixture corresponding to 10 cc. of urine is heated on the water bath until the ammonia is expelled, and the urea is then estimated as usual. In a second portion not treated with baryta solution the ammonia is determined volumetrically with a standard sulphuric acid solution, each cc. of which corresponds to 11.32 mgrm. of ammonia or 20 mgrm. of urea. (500 cc. of such an acid must contain 16.333 of monohydrated sulphuric acid.)

b. A definite volume of the urine treated with baryta solution is distilled, and the ammonia which passes over is collected in a known volume of standard sulphuric acid. By means of a standard sodic hydrate, which is of corresponding strength to the sulphuric acid, the rest of the acid is titrated back, and the number of cc. saturated by ammonia thus found is calcu-

lated for urea. One cc. of sulphuric acid corresponds to 20 mgrm. of urea. The results by this second method are more exact than by the first.

Kletzensky found by a series of comparative investigations that small amounts of other nitrogenous substances besides urea were precipitated from the urine by mercuric nitrate, so that naturally the amount of urea fell a little too high. These unknown substances may be separated by precipitation with a solution of sugar of lead and their disturbing influence removed. On the average this error amounts to about two per cent., for Kletzensky obtained as a mean of several urea estimations, which he performed once in the ordinary manner and again after previous precipitation with sugar of lead, 0.593 grm. of urea in 10 cc. of urine instead of 0.580 grm. This error is so small, that in ordinary urinary analysis the tedious process of precipitating the urine previously acidulated with acetic acid with a solution of sugar of lead may safely be omitted. These substances are also said to yield ammonia on boiling with sulphuric acid, and to have a disturbing influence on the urea determination by the method of Ragsky and Heintz.\*

If the urine contains sarkosin, as is the case after the internal use of this substance, the precipitation of the urea present at the same time is completely prevented, both in the neutral as well as in the alkaline solution. (E. Baumann and J. von Merling.)† The same is true, according to E. Salkowski,‡ of methylhydantoin, and according to Schultzen and Nencki of acetamid also. If a solution containing equal molecules of urea and sarkosin or methylhydantoin is titrated, at first no precipitate occurs; but if the titration is carried farther, the end reaction occurs far later than would be caused by the urea present; indeed, the latter appears to be present in double the amount that it really is. (E. Salkowski.) In these cases Liebig's method is wholly useless.

Lastly, the fact should be remembered that allantoin also, like urea, is precipitated by mercuric nitrate. The method described above, therefore, will cause an error when allantoin occurs in the urine also. The error which is caused by the con-

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\* Prager Vierteljahresschrift, 1855, ii. p. 83.

† Berichte d. deutsch. chem. Gesellschaft, Band 8, p. 588 und 630.

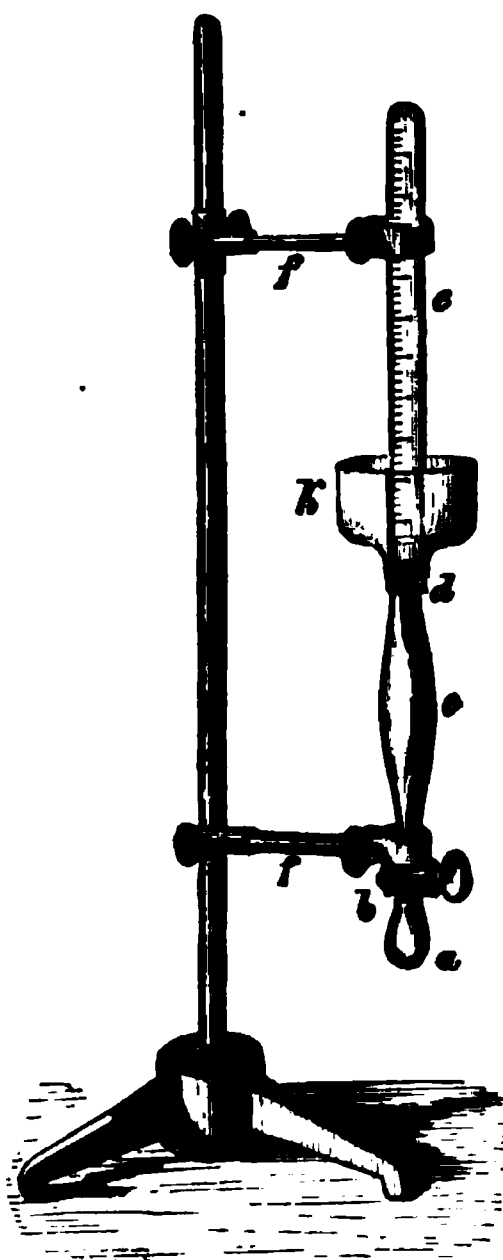
‡ Ibid.

stant presence of kreatinin in the urine, is more perceptible, though always less, for, as I have found, this body is also precipitated by mercuric nitrate. The daily quantity of kreatinin amounts to 0.8 to 1 gm. under normal circumstances.

The excellent methods for the quantitative determination of urea given by Heintz\* and Ragsky,† as well as by Bunsen,‡ are not, however, entirely free from these and similar sources of error, and since they are considerably more detailed and demand more time than Liebig's method, they are employed in practice less frequently.

#### ESTIMATION OF UREA BY THE KNOP-HÜFNER METHOD.§

FIG. 28.



A. *Principle.* As was mentioned above under urea, § 2, D, 7, hypobromite of sodium decomposes urea into carbonic acid, nitrogen, and water. The carbonic acid is very quickly absorbed by the lye, so that the urea can be quantitatively determined by the direct measurement of the nitrogen. One gm. of urea yields 370 cc. of nitrogen measured at 0° C., and 760 mm. barometric pressure.

B. *Preparation of the Solution of Hypobromite of Sodium.* 100 gm. of sodic hydrate are dissolved in 250 cc. of water, and 25 cc. of bromine are added after the solution has become perfectly cold. 50 cc. of this solution, diluted with 200 cc. of water, are sufficient to develop 130 to 150 cc. of nitrogen from a chloride of ammonium solution.

C. *Performance.* The decomposition of urea takes place very well in Hüfner's apparatus, shown in fig. 28. A bellied vessel holding about 100 cc. is in solid connection with a small vessel, *a*, which holds at most from 5 to 8 cc., by

\* Poggend. Annal., Band 66, p. 114.

† Annalen d. Chem. u. Pharm., Band 56, p. 29.

‡ Annalen d. Chem. u. Pharm., Band 65, p. 375.

§ Journ. f. pr. Chem., N. F., Band 3, p. 1.

means of a tolerably wide mouth of 1.5 cm. in diameter. Between the two, at *b*, there is inserted a tightly-fitting glass stop-cock, with a bore 8 or 10 mm. wide. The upper, smaller end of the larger vessel, *d*, is tightly surrounded by the neck of a glass dish, *k*, which has a width of 1 dm. and a depth of 4 or 5 cm., and rises up into its centre about 1 cm. This end also extends into the opening of a eudiometer, *e*, which stands over it. The eudiometer is about 30 cm. long, 2 cm. wide, and is divided into  $\frac{1}{2}$  cc. The whole apparatus is properly attached to an iron stand, *f, f*.

The operation is now carried out as follows: With the aid of a funnel having a long neck, the glass, *a*, together with the bore of the stop-cock, is filled with the urea solution, 2 or 3 cc. of urine being quite sufficient; 10 cc. of urine are diluted to 40 or 50 cc., and from 8 to 12 cc. of this dilute urine are used for each analysis. The cock is then closed, and a mixture of equal parts of lye and distilled water is poured into the larger vessel, *c*, up to the edge. In the dish, *k*, there is placed a layer of saturated chloride of sodium solution, or, better still, the same bromine lye, 2 cm. deep, which serves as a shutting-off fluid. During this time only a few air bubbles are evolved from *c*; when they have disappeared, the eudiometer filled with water is turned upside down over *d*, and, when it is fastened, the reaction may commence. The stop-cock, *b*, is now turned at once, and the two fluids are thus brought together suddenly. The heavy lye quickly sinks into the lower vessel and brings about decomposition of the urea with active evolution of nitrogen which collects in the eudiometer. If an accurate determination is not required, the experiment may be interrupted after five minutes; in the other case it is advisable to wait a few hours. The eudiometer is then taken from the dish, *k*, its opening closed with the thumb, and it is carried to a cylinder filled with water and treated in measuring the gas according to Dumas's rule for the determination of nitrogen.

It is well to employ Knop's lye as fresh as possible.

The calculation is carried out according to the following formula, since 1 gram. of urea yields 370 cc. of nitrogen at 0° C. and 760 mm. pressure:

$$p = \frac{100 \, v \, (b - b')}{760.370 \cdot a \, (1 + 0.003665 \, t^{\circ}. )}$$

$a$  = the volume of urine employed.

$v$  = the volume of gas read off.

$b$  = the height of the barometer.

$t$  = temperature.

$b'$  = the tension of aqueous vapor for the temperature  $t$ .

Of the other constituents of the urine, uric acid and kreatin also give up a portion of their nitrogen; but with the small amounts of these substances which the urine contains the error caused by them is very small.

Ivon\* produced the decomposition in a simpler apparatus. It consists of a small glass tube 40 cm. high, which is divided into  $\frac{1}{10}$  cc., and has a glass stop-cock at its upper part, above which there is a short piece of tubing of the same diameter, also divided. The apparatus is open at both ends. To determine the urea the lower end is sunk into a cylinder of mercury wide at the top; then 2 or 3 cc. of urine are placed in the upper part, and by opening the stop-cock it is allowed to flow into the lower part; it is afterward washed with a little sodic hydrate and the upper piece of tubing is filled with a solution of hypobromite of sodium. (Ivon uses the following solution: 30 gm. of sodic hydrate, 5 gm. of bromine, and 125 gm. of water.) If this is allowed to flow into the lower receiver by a quick but careful turning of the stop-cock, the development of gas begins immediately and is finished after five or six minutes. The nitrogen is then measured as above, reduced for pressure and temperature, and calculated for urea.

This method excels from its great simplicity, rapid performance, and sufficient accuracy.

#### BUNSEN'S METHOD MODIFIED BY G. BUNGE†

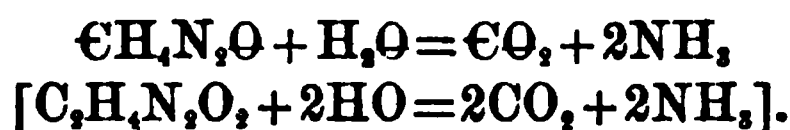
50 cc. of urine are mixed with 25 cc. of an ammoniacal solution of chloride of barium as concentrated as possible; it is filtered through a dry filter, and 15 cc. of the filtrate, corresponding to 10 cc. of urine, are put into a strong glass tube sealed at the bottom, and containing about 3 gm. of solid, pure

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\* Buletin de la Société chim. de Paris, 19, p. 8.

† Zeitschrift f. analyt. Chem., Band 13, p. 128.

chloride of barium. In introducing the mixture of urine care must be taken to keep the walls above the fluid dry. The tube is then thoroughly sealed over a lamp an inch to an inch and a half above the fluid, and heated five or six hours to 200° C. After it has cooled, the upper part of the tube is broken off, the contents thrown on a filter and thoroughly washed with water. The glass tube, on the inside of which small portions of carbonate of barium are frequently firmly adherent, is also thoroughly washed out, the whole amount of the carbonate of barium is dissolved in hydrochloric acid, filtered if necessary, and the barium precipitated by sulphuric acid as barium sulphate. After a time the sulphate of barium is collected on a filter, washed, ignited, and weighed. In the above treatment the urea is decomposed according to the following formula:



A molecule of  $\text{BaSO}_4$  corresponds, therefore, to a molecule of urea. 233 parts by weight of barium sulphate correspond to 60 parts by weight of urea.

The extractive matters of the urine have no influence. But albumen and sugar heated with water to 200° C. develop large amounts of carbonic acid; when the urine contains albumen and sugar, therefore, the method is not applicable. (Hoppe-Seyler.)

## § 66. ESTIMATION OF THE CHLORINE (CHLORIDE OF SODIUM).

### I. MOHR'S METHOD.

*A. Principle.* The principle of this method is easily understood. The urine filtered and acidulated with nitric acid is treated with a standard solution of nitrate of silver as long as a precipitate is produced; but it is difficult to hit this point exactly without filtering, wherefore the method loses a little in convenience and accuracy. Mohr proposed, therefore, to add a few drops of a solution of neutral chromate of potassium in the titration of fluids containing chlorine, and then to perform the analysis as usual. The end reaction with this modification manifests itself in a beautiful and striking way, since, when all of the chlorine is precipitated by the solution of nitrate of silver, the next drop

gives a beautiful red precipitate of chromate of silver. But this change requires neutral or at least faintly alkaline fluids, and on no account should there be any free acid present on account of the ready solubility of the chromate of silver in acids. But though this method is admirable in pure fluids containing chlorine, in its application to the urine considerable difficulties are encountered, which are caused by the necessity of its having a neutral reaction. Many comparative experiments which I conducted first by Liebig's method, then by Mohr's, and finally gravimetrically, gave me always too high a result when titrated with a nitrate of silver solution after the addition of chromate of potassium. The reason of this is readily seen. If the titration is carried out exactly according to Mohr's method, and a few drops of a solution of chloride of sodium are now added until the color of the fluid has become pure yellow again, in order to decompose the chromate of silver, the precipitate which is formed now is not pure chloride of silver. If, the light having been shut off, it is filtered, and after washing treated with cold dilute nitric acid, it becomes colored, and a not inconsiderable amount of silver may be detected in the filtrate by hydrochloric acid. There is no doubt that oxide of silver in a neutral fluid is precipitated by coloring and extractive matters, and also by uric acid, wherefore an inexactness of the method must be the result. Phosphoric acid does not disturb the result, since chromate of silver is precipitated before the phosphate. (Compare § 13, C, 4.) (Analytical Experiments.)

Even in acid solutions the coloring and extractive matters, etc., are not wholly without influence, and I prefer, therefore, to completely destroy these substances according to Mohr's proposition by evaporating the urine after the addition of a little pure nitrate of potassium and heating the residue to a dull red heat.

#### B. *Preparation of the Solutions.*

1. *Standard Nitrate of Silver Solution.* This solution must contain 18.469 grm. of silver to the liter, so that each cc. corresponds to 10 mgrm. of chloride of sodium or 6.065 mgrm. of chlorine. Therefore 18.469 grm. of chemically pure silver are dissolved in nitric acid, the solution is evaporated to dryness on the water bath, heated until all of the free nitric acid is removed, the residue taken up with distilled water, and the solution thus obtained diluted to a liter. If chemically pure fused



nitrate of silver is at our disposal, we can simply weigh off 29.075 grm., dissolve it in water, and dilute it to a liter.

2. *Chromate of Potassium Solution.* A cold saturated solution of neutral chromate of potassium.

*C. Performance in Urine.*

5 or 10 cc. of urine are introduced into a small platinum dish, 1 or 2 grm. of nitrate of potassium free from chlorine are added, and it is evaporated to dryness on the water bath. The residue is then heated over a free flame at first gently, afterward stronger, until the carbon is completely oxidized and the residue is obtained as a white, fused, saline mass. The operation readily and surely succeeds in this way, since the great excess of nitrate of potassium greatly diminishes the deflagration, which is otherwise violent. The perfectly white saline mass is then dissolved in a little water, the solution is turned into a beaker, and the platinum dish carefully rinsed with water from a wash bottle. Very dilute pure nitric acid is added drop by drop to the alkaline fluid until a feebly acid reaction has resulted, which is then neutralized by as much precipitated calcic carbonate as can be contained upon the point of a knife. The excess of calcic carbonate is not filtered off before the titration, since it in no wise prevents the end reaction. Two or three drops of the solution of chromate of potassium are added to the mixture, and then the neutral silver solution is allowed to flow into it with constant stirring, until a distinct reddish tinge is produced, which is permanent also after stirring. The reaction is very beautiful; the fluid, at first of a light canary-yellow color, shows in the places where the silver solution falls red spots which disappear on stirring as long as chloride of sodium is still present. But as soon as the latter is completely decomposed by the addition of the silver solution, the next drop shows a permanent reddish tinge of chromate of silver, which indicates the end of the experiment.

Each cc. of the silver solution used up to this point indicates 10 mgrm. of chloride of sodium or 6.065 mgrm. of chlorine. If, for example, to 5 cc. of urine we have used 5 cc. of the solution of silver, they contain 50 mgrm. of NaCl, and 1,000 cc. of the urine, 10.0 grm. NaCl or 6.065 grm. chlorine.

Pribram\* destroys the organic matters at a boiling tem-

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\* Zeitschrift für analyt. Chemie, Band 9, p. 428.



perature with permanganate of potassium. 10 cc. of urine are heated with 50 cc. of permanganate of potassium solution (1 or 2 grm. of the salt in a liter), and the chlorine in the filtrate is determined as usual. I have not obtained good results by this method. In my experiments 10 cc. of normal urine often decomposed four times as much chemically pure permanganate of potassium as Pribram states. There is found in this way, as is easy to prove, a considerable amount of oxalic acid, and the titration with the silver solution not rarely gave, especially in concentrated urines, considerably more chlorine in the clear, tolerably dilute filtrate than the method described above, which I, therefore, unconditionally prefer. (Analytical Experiments.)

Liebig's method\* of estimating chlorine with mercuric nitrate, aside from the fact that in many cases it fails, unless carried out very exactly, frequently gives absolutely erroneous results. In regard to easy manipulation and certain success, it is far behind the method with silver; therefore I content myself with referring to the original treatise in regard to it.

1. *Modification in Urine containing Iodine and Bromine.*

On account of the readiness with which the iodide and bromide of potassium go over into the urine, these substances must be considered in an accurate estimation of the chlorine. According to Salkowski, this error is most easily avoided as follows: 10 cc. of the urine are evaporated with nitre as usual, and ignited, the residue is dissolved in water, acidified with sulphuric acid, and the iodine removed by shaking with bisulphide of carbon. If the nitrite which forms on fusing does not suffice to set free all of the iodine present, it is advisable to add a few drops of a solution of nitrite of potassium to the acidulated urinary fluid before it is shaken with bisulphide of carbon. The aqueous solution is finally neutralized with carbonate of sodium, evaporated and titrated with nitrate of silver as usual

II. METHOD OF J. VOLHARD AND A. FALCK.

A. *Principle.* This method is founded on the behavior of soluble sulphocyanides toward solutions of silver and ferric salts. Soluble sulphocyanides produce in silver solutions a white precipitate similar to chloride of silver, which is insoluble in dilute

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\* Annalen d. Chem. u. Pharm., Band 85, p. 297.

nitric acid. A like precipitate of sulphocyanide of silver with a solution of nitrate of silver is given by the blood-red solution of sulphocyanide of iron, and the color of the latter at last completely disappears. If, therefore, a solution of sulphocyanide of potassium is added to an acid solution of nitrate of silver to which a little ferric sulphate has been added, every drop of the sulphocyanide solution at first produces a blood-red cloud, which, however, quickly disappears again on stirring, while the fluid becomes milk-white. It is not until all of the silver is precipitated that the red color of the sulphocyanide of iron remains permanent, and at the same time the end of the experiment is reached. The reaction is extremely delicate, so that this method is not inferior to the first in point of sensitiveness, and it has the advantage that the titration can be undertaken in an acid solution.

*B. Preparation of the Solutions.*

1. *Standard Nitrate of Silver Solution.* Description, see § 66, 1, B, 1. Each cc. corresponds to 10 mgrm. of chloride of sodium or 6.065 mgrm. of chlorine.

2. *Solution of Iron Oxide.* A cold saturated solution of crystallized ferric alum free from chlorine, or a solution of ferric sulphate, which contains about 50 gm. of iron oxide in the liter, is used.

3. *Standard Solution of Sulphocyanide of Potassium.* Since sulphocyanide of potassium cannot be easily weighed accurately, 10 gm. are dissolved in a liter of water and this solution is standardized by the silver solution. For this purpose 10 cc. of the silver solution are measured off, 5 cc. of the iron solution are added, and then pure nitric acid is added drop by drop until the mixture appears colorless. If the sulphocyanide of potassium solution is then allowed to flow into it from a burette, every drop at first gives a blood-red color, which immediately disappears on stirring. When all of the silver is precipitated as sulphocyanide of silver, the next drop of the sulphocyanide of potassium solution gives a permanently red color to the fluid which indicates the end of the experiment. If, for example, to 10 cc. of the silver solution 9.6 cc. of the sulphocyanide of potassium solution have been used before the red coloration is permanent, 960 cc. of the latter are measured off, and this is diluted with 40 cc. of water to make a liter. Both solutions

must now be equivalent, which is to be determined by titrating again.

C. *Performance of the Analysis with Urine.* 5 or 10 cc. of urine after the addition of 1 or 2 grm. of nitrate of potassium free from chlorine are evaporated and ignited as mentioned above, § 66, 1, C. Since the nitrous acid which is formed in this operation prevents the end reaction, the fused saline mass is dissolved in water, acidulated with nitric acid, and then the chlorine is precipitated with an excess of the standard silver solution. After this mixture has been warmed on the water bath for a time to completely remove the nitrous acid it is allowed to cool, 5 cc. of the iron solution are added, and then sulphocyanide of potassium solution equivalent in strength to the silver solution is added while constantly stirring until the excess of the silver added is precipitated, which point is recognized by the permanent red color of the mixture. The difference then between the number of cc. of the silver and sulphocyanide solutions corresponds to the chlorine contained in the urine. If, for example, at first 12 cc. of the silver solution were added to 10 cc. of urine, and 4 cc. of the sulphocyanide solution were required to titrate back the excess, the amount of chlorine in the urine corresponded to  $12 - 4 = 8$  cc. of the silver solution  $= 8.0$  grm. of chloride of sodium or 4.852 grm. of chlorine in the liter of urine.

#### § 67. ESTIMATION OF PHOSPHORIC ACID.

A. *Principle.* If a hot solution of a phosphate dissolved in water or acetic acid is treated with a solution of acetate or nitrate of uranium, when free acetic acid is present, a precipitate of the phosphate of uranium occurs at once. If the solution contains salts of ammonium in large amount, the precipitate also contains ammonia. The phosphate of uranium thus precipitated contains 80.09 parts of uranium oxide to 19.91 parts of  $\text{PO}_5$ , and appears as a whitish-yellow precipitate with a faint greenish tinge, which is completely insoluble in water and acetic acid, but is soluble in the mineral acids. Since the precipitate is slimy and does not easily settle, the end of the reaction cannot be perceived in the fluid by stopping the precipitation; therefore, to ascertain whether all of the phosphoric acid is

precipitated, a slight excess of uranium oxide must be added, which can be detected with ease by the very delicate reaction of the uranium salts with ferrocyanide of potassium. Uranium salts, as is well known, give a reddish-brown precipitate with ferrocyanide of potassium, by which the slightest traces of uranium oxide are indicated by a corresponding reddish-brown coloration of the fluid. The uranium oxide once precipitated is not decomposed by ferrocyanide of potassium, as is the freshly precipitated ferric phosphate; therefore to test for an excess of uranium a drop of the mixture may be brought directly in contact with the solution of ferrocyanide of potassium. If there is no free oxide of uranium present, the mixture does not become colored, but the slightest excess of oxide of uranium is most certainly recognized by a corresponding red color. Moreover, phosphate of uranium is a perfectly stable compound, and in a solution containing an excess of uranium does not, like ferric phosphate, change into a more basic compound; therefore, when the end reaction has once distinctly occurred, it may be produced again even after standing for days, which by the old method with ferric chloride was not the case even after a few minutes, for which reason the latter method is highly unsatisfactory and faulty.

In the presence of acetate of sodium, however, the reaction of the ferrocyanide of potassium on uranium salts is not so delicate as in pure aqueous solutions. It is easy to be convinced of this if 50 cc. of water and 50 cc. of a solution of acetate of sodium, which contains 0.5 gram of the latter and 1 gram of free acid, are treated side by side with 0.2 cc. of the same solution of uranium and both tested with ferrocyanide of potassium. The distilled water will immediately show a very distinct brown color, while the solution of acetate of sodium gives a much feebler reaction, which gradually grows darker after a time. If the amount of acetate of sodium is large, the reaction at first entirely fails and appears only after a long time on the further addition of ferrocyanide of potassium.

*This circumstance is of the greatest importance, since in the titration of phosphoric acid with uranium salts (for example, in 50 cc. of urine) sometimes more and sometimes less acetate of sodium is added, so that sometimes more and sometimes less uranium solution will be required with the same amount of phosphoric acid to obtain the end*

reaction with ferrocyanide of potassium, and an error will thus be committed, which, however, is readily obviated by always taking a like volume of fluid and treating this constantly with the same amount of acetate of sodium before the titration.

**B. Preparation of the Solutions.**

1. *Standard Phosphoric Acid Solution.* It is well to have this of such a concentration that 50 cc. of it contain 0.1 gram.  $\text{PO}_5$ , so that it approaches normal urine in regard to the amount of phosphoric acid as nearly as possible. It can be readily prepared from chemically pure, well-crystallized phosphate of sodium which has not been exposed to the air. The pure crystals are rubbed very fine, dried by pressing between filter paper, 10.085 gm. are accurately weighed off, and dissolved to a liter. 50 cc. then contain exactly 0.1 gm.  $\text{PO}_5$ .

2. *Solution of Acetate of Sodium.* I have convinced myself by many experiments that 0.5 gm. of acetate of sodium is sufficient in all cases for 50 cc. of urine. Therefore 100 gm. of acetate of sodium are dissolved in 900 cc. of water, and this solution is brought up to a liter by 100 cc. of concentrated acetic acid. In the titration 50 cc. of urine are treated with 5 cc. of this acid solution of acetate of sodium.

3. *Uranium Solution.* Pure commercial oxide of uranium or yellow double carbonate of uranium and sodium is dissolved in pure acetic acid, especially free from empyreumatic matters, the solution is diluted and it is standardized with the phosphate of sodium solution a. I have found it advantageous to so arrange the uranium solution that 1 cc. of it precipitates and indicates only 0.005 gm. of phosphoric acid. 50 cc. of our solution of phosphoric acid, a = 0.1 gm. of  $\text{PO}_5$ , and therefore will need exactly 20 cc. of the uranium solution, which must contain first 0.4023 gm. of oxide of uranium to precipitate the  $\text{PO}_5$ , and second, a slight excess of oxide of uranium to indicate the end reaction. Therefore 50 cc. of the phosphoric acid solution a (0.1 gm.  $\text{PO}_5$ ) are measured off, allowed to flow into a beaker, 5 cc. of the acid solution of acetate of sodium b are added to it, and it is heated on the water bath to 90° or 100° C. The uranium solution is now allowed to flow into it, and it is tested after each  $\frac{1}{2}$  cc. for the end reaction. For this purpose one or two drops of the mixture are spread out on a white porcelain surface, and then a small drop of a feebly yellow-colored solution of ferro-

cyanide of potassium is introduced into its centre by means of a slender glass rod. Even if there is only a trace of an excess of oxide of uranium in the mixture, a reddish-brown island will form where the ferrocyanide of potassium solution is introduced, and, surrounded by the colorless or faint-yellow fluid, can be perceived with the greatest distinctness. I prefer this method to any other; if after repeated testing and renewed addition of uranium solution a faint end reaction is finally obtained, it is again heated a few minutes on the water bath and tested once more. If now the reaction appears distinctly, the experiment is ended. 50 cc. of our phosphoric acid solution should require 20 cc. of the uranium solution; each cc. of the latter should, therefore, precipitate and indicate 5 mgrm. of  $\text{PO}_5$ . Supposing we had used 18.0 cc. of uranium solution to 50 cc. of the  $\text{PO}_5$  solution, we must add 20 cc. of water to every 180 cc. of the solution. Therefore one liter of the uranium solution is measured off, the necessary amount of water is calculated and added. In our case 111.2 cc. of water must be added to 1,000 cc. of the uranium solution, in order to obtain the desired concentration. It is well, however, not to add the calculated amount of water at once, but a little less, test again with the phosphoric acid solution, and finally complete the uranium solution. If, for example, we have used the second time 19.8 cc. of the uranium solution to 50 cc. of the  $\text{PO}_5$  solution (0.1 gm. of  $\text{PO}_5$ ), we now add to every 198 cc. of the same 2 cc. of water, and make a new and thereby final test with the phosphate of sodium solution. Such a uranium solution, each cc. of which precipitates 5 mgrm. of  $\text{PO}_5$ , and which at the same time contains a slight excess of oxide of uranium for the end reaction, must contain 20.3 gm. of pure oxide of uranium in the liter. (Equivalent of uranium = 60.)

*C. Performance with the Urine.*

*a. Estimation of the Total Phosphoric Acid.*

1. 50 cc. of urine, previously filtered, are put into a beaker, 5 cc. of the acetate of sodium solution are added, heated on the water bath, and then the uranium solution is allowed to flow into it from a Mohr's burette divided into  $\frac{1}{10}$  cc. When the precipitate no longer increases, which can be observed quite readily if the uranium solution is allowed to flow slowly down the side of the glass without stirring, the test is performed.



For this purpose one or two drops of the mixture are spread out on a white porcelain surface and a drop of a faintly yellow-colored solution of ferrocyanide of potassium is added to the centre of it by means of a slender glass rod. If there is a slight excess of oxide of uranium present, where the ferrocyanide of potassium solution is added an island of reddish-brown color is formed, which surrounded by the colorless or slightly yellow fluid may be observed with the greatest distinctness. If a feeble end reaction has taken place, the heat is continued for a short time (1 or 2 minutes) over the water bath and it is tested again; if now the reaction remains distinct, *if the color obtained corresponds to the tint at which the uranium solution was originally standardized*, the experiment is ended. But in the other case the addition of the uranium solution is continued until the end reaction comes out distinctly and is permanent. But if through the careless addition of the uranium solution the proper end point shall have been exceeded, and therefore, if on the addition of the ferrocyanide of potassium a deep brown color occurs immediately, then, according to circumstances, 10 or 20 cc. of urine are added to the mixture and the titration is continued with a more careful addition of the uranium solution until the right tint is reached. As was observed above, acetate of sodium retards the reaction of ferrocyanide of potassium with oxide of uranium, therefore the color gradually becomes darker, and care must be taken not to make a mistake. At all events we should accustom ourselves to regard the first very feeble brownish coloring in the centre of the drop, which can be brought out again in the same tint after further heating on the water bath (2 or 3 minutes), as the end of the experiment, though after the lapse of 10 or 15 minutes the brown color will increase in intensity. Pincus and Bödecker, both of whom likewise proposed the oxide of uranium for the same purpose, perform the analysis in the cold, but I unconditionally prefer a hot fluid, since the complete separation of the phosphate of uranium takes place very much quicker in hot fluids. If to 50 cc. of urine, for example, 20 cc. of uranium solution have been required to produce the feeble but permanent reaction on heating, it contains 0.100 grm. of  $\text{PO}_5$ , which can readily be reckoned for the twenty-four hours' amount.

2. The results are more exact when all of the phosphoric acid

is precipitated from the urine by a solution of magnesium, and the phosphoric acid is titrated as above in the washed precipitate. For this purpose 50 cc. of urine are precipitated with magnesium mixture (a clear mixture of sulphate of magnesium, chloride of ammonium, and ammonia), and are allowed to stand several hours for the complete separation of the precipitate. The ammonio-magnesian phosphate is collected on a small filter, washed with water containing ammonia (one part of ammonia and three parts of water), and after the filter has been broken through it is washed into a beaker. After heating on the water bath acetic acid is added, drop by drop, until it is completely dissolved, it is diluted to 50 cc. with water, 5 cc. of the acetate of sodium solution are added, and the fluid is titrated with the uranium solution just as recommended above. This roundabout way is necessary only in the rarest cases, since the results are very satisfactory also when the urine is directly analyzed. Generally a few tenths of a cubic centimeter less of the uranium solution would be required by this second method in one and the same urine, which in the daily amount of urine of 1,500 cc. amounts to about 0.15 or 0.2 gm.  $\text{PO}_5$ .

*b. Determination of the Phosphoric Acid combined with the Alkaline Earths.*

In order to determine only the amount of phosphoric acid combined with the alkaline earths, 100 or 200 cc. of the filtered urine, according to its concentration, are treated with ammonia until the reaction is alkaline, and it is then allowed to stand twelve hours. The earthy phosphates separated during this time are collected on a filter, and washed with water containing ammonia (one part of ammonia and three parts of water). When this is accomplished the filter is broken through, the precipitate washed into a beaker, and dissolved by the aid of heat in as little acetic acid as possible, and the phosphoric acid titrated, after 5 cc. of the acetate of sodium solution have been added and the whole volume has been brought to 50 cc., with the uranium solution as described under a.

**Example :**

50 cc. required 18.4 cc. of the uranium solution for the precipitation of the total phosphoric acid = 0.092 gm. phosphoric acid. In 1,000 cc. there were, therefore, 1.840 gm. To determine the phos-



phoric acid combined with the alkaline earths there were required for 100 cc. of urine 6 cc. of uranium solution = 0.03 gm. of  $\text{PO}_4$ . In 1,000 cc. there were, consequently, 0.300 gm.

The urine contains then

- |   |             |
|---|-------------|
| a. Total $\text{PO}_4$ ,                            | = 1.840 gm. |
| b. $\text{PO}_4$ combined with the earths = 0.300   | “           |
| <hr/>   |             |
| c. $\text{PO}_4$ combined with the alkalies = 1.540 | “           |

### § 68. ESTIMATION OF THE DEGREE OF ACIDITY.

*A. Principle.* Since the acid reaction of a urine does not depend alone on the acid phosphate of sodium, but the presence of free acids may also contribute to it, as, for example, lactic acid, etc., we must be contented in estimating the amount of acidity to compare its power of saturation with that of some known acid. Crystallized oxalic acid is selected for this purpose, and in this determination, therefore, we must establish how much oxalic acid the free acid present in a stated amount of urine corresponds to. We gain our object by accurately neutralizing the known amount of urine with an alkaline solution, each cc. of which corresponds to a fixed amount of oxalic acid; sodic hydrate solution is best for this purpose, since it does not lose its efficacy by volatilization as ammonia does, and at the same time it shows the point of neutralization very distinctly.

#### *B. Preparation of the Solutions.*

1. *Standard Oxalic Acid Solution.* This serves us for standardizing the sodic hydrate solution. It is prepared by dissolving 1 gm. of pure oxalic acid which has not effloresced, and diluting it to 100 cc. Each 10 cc. of this solution contain 100 mgrm. of oxalic acid.

2. *Tincture of Litmus.* 3 gm. of litmus are digested for a long time with 20 gm. of water, and the deep blue solution obtained is filtered.

3. *Sodic Hydrate Solution.* This is prepared as usual from carbonate of sodium and quicklime, and then its strength is determined with the oxalic acid solution, a. Each cc. must indicate 10 mgrm. of oxalic acid.

10 cc. of the oxalic acid solution are accurately measured by

means of a pipette, it is allowed to flow into a small beaker, and is colored distinctly red by a few drops of the tincture of litmus. The glass is then put on a white background, and the dilute sodic hydrate dropped into it until the fluid has become blue again. This point can be observed with the greatest distinctness, since the transition of the red color to the blue takes place quite suddenly. Suppose that 6 cc. of the sodic hydrate solution have been required for this purpose, they correspond to 100 mgrm. of oxalic acid; we therefore add 400 cc. of water to 600 cc. of the sodic hydrate and thus obtain a liter of alkaline solution, each cc. of which corresponds exactly to 10 mgrm. of oxalic acid. We now assure ourselves of the accuracy of our dilution by a second titration; if the blue color takes place after the last drop of 10 cc. has been added, then the sodic hydrate may be used for determining the acid in the urine.

*C. Performance.*

On account of the color of the urine itself it is impossible to add the tincture of litmus directly to it in titration, since the change from red to blue cannot be observed with sharpness in a colored fluid. With urine, therefore, we must have recourse to litmus paper in order to determine the point of saturation, and must perform the analysis as follows:

After 50 or 100 cc. of urine are measured off and introduced into a beaker, the standard sodic hydrate is added drop by drop. After each  $\frac{1}{4}$  cc. used, a drop of the fluid is taken out with a glass rod and placed on a small piece of sensitive blue litmus paper. If the spot where the drop lies becomes red after a few seconds, the addition of sodic hydrate is continued until no more reddening of the paper is observed. A drop is then put on red litmus paper, and if it is made blue, the volume of sodic hydrate which was used is noted, and the experiment is repeated with a new quantity of the urine, but a few drops less are added; by frequent testing the point of saturation is very accurately determined.

§ 69. ESTIMATION OF THE SULPHURIC ACID.

*A. Principle.* The method of estimating sulphuric acid depends simply on the addition of a solution of chloride of barium of known strength to a definite quantity of urine, as long as a

precipitate of sulphate of barium is produced by it. But it is to be noticed that as soon as an amount of chloride of barium exactly equivalent to the quantity of sulphuric acid has been added to a fixed volume of urine feebly acidified with hydrochloric acid, a so-called neutral point occurs in which the filtrate shows a slight cloudiness, both with sulphuric acid and with a solution of chloride of barium. In the solution thus formed chloride of potassium, chloride of barium, and sulphate of potassium must be considered to be in a certain condition of equilibrium; now, if chloride of barium or sulphate of potassium is added, the equilibrium is destroyed and a precipitation of sulphate of barium results. In the titration of sulphuric acid in urine with a solution of chloride of barium, either the latter can be added until the neutral point is reached, that is, until in the filtrate both by another drop of the chloride of barium solution, and in another specimen by a drop of a solution of sulphate of potassium, a faint cloudiness is produced, or until only a slight excess of barium is indicated in the filtrate by sulphate of potassium.

The solution of chloride of barium must naturally have a different concentration, according as the one or the other end reaction is chosen. If the titration is carried to the neutral point, it is well to make the solution of chloride of barium of such a strength that 1 cc. of it contains an amount of barium exactly equivalent to 10 mgrm. of sulphuric acid; but in the second case, the barium solution must contain a slight excess of barium for each cc. to precipitate 10 mgrm. of  $\text{SO}_4$ , and to indicate the end reaction by a slight barium reaction in the filtrate. I have convinced myself that the neutral point can be attained quite readily, and that the results when the titration is carried to this point are quite satisfactory; and, therefore, I prefer to regard the titration of sulphuric acid as ended once for all, when in two specimens of the clear filtrate an equally faint cloudiness is produced by chloride of barium and by sulphate of potassium. Mulder first called attention to this neutral point, in the titration of a solution of silver by chloride of sodium.

#### B. *Preparation of the Solutions.*

1. *Chloride of Barium Solution.* This solution must be so concentrated, that 1 cc. of it precipitates exactly 10 mgrm. of

sulphuric acid. It is prepared simply by dissolving 30.5 gm. of powdered, crystallized chloride of barium which has been dried in the air, and diluting the solution to a liter. 1 cc. then corresponds to 10 mgrm of anhydrous sulphuric acid.

2. *Solution of Sulphate of Potassium.* This must be exactly equivalent to the chloride of barium solution; it is prepared by dissolving 21.778 gm. of powdered, chemically pure, sulphate of potassium dried at 100° C., and diluting the solution to a liter. 1 cc. then contains 10 mgrm. of sulphuric acid, and is exactly equivalent to the solution of chloride of barium.

C. *Performance.* 100 cc. of the urine to be examined are put into a narrow long-necked flask (fig. 29), treated with twenty or thirty drops of hydrochloric acid, and heated on the water bath; then 5 or 8 cc. of the chloride of barium solution are allowed to flow into it from a burette and to stand until the sulphate of barium has settled. At a boiling temperature it becomes thick quite rapidly and then deposits very well. When the fluid has become clear another cc. of the chloride of barium solution is added, it is heated, and ten or twelve drops of the urine are filtered through a small filter the size of a thimble into a very small narrow test tube about two inches long, and tested to see if there is any further precipitation by the chloride of barium or not. If the latter is the case, a few drops of sulphate of potassium solution are added to a second specimen of the filtrate by which an excess of the baric chloride solution is shown. But if in the first specimen we still get a distinct cloudiness with the baric chloride solution, the fluid is poured back again into the flask, the filter and tube are rinsed with a little water and this is added to the urine also. If thus far about 8 cc. of chloride of barium solution have been used, 1, 2, 3, or 4 more are added, according to the intensity of the reaction, which by a little practice can readily be estimated by the degree of cloudiness which takes place at the first test, the whole is heated to boiling, a few drops are again filtered off for testing, and this is continued until at last there is no more cloudiness produced in the filtrate by chloride of barium. If this is the case after using, for example, 13 cc., and if sulphate of potassium

FIG. 29.



now in a new test shows a distinct excess of barium, we know that the right point must lie between 12 and 13 cc., and the 100 cc. of urine must contain between 120 and 130 mgrm. of sulphuric acid.

100 cc. of the urine are, therefore, measured off anew, treated with 20 or 30 drops of hydrochloric acid, 12 cc. of the chloride of barium solution are added immediately, heated, and a few drops of the filtrate tested with  $\frac{1}{10}$  cc. of the baric chloride solution. If a distinct cloudiness takes place immediately, the filtrate and the original fluid are united again,  $\frac{2}{10}$  cc. more of the baric chloride solution are added, the filtrate is again tested, and this is continued till at last the chloride of barium solution shows only a very faint cloudiness after several seconds. If a second specimen of the filtrate is now tested with a few drops of the sulphate of potassium solution, it will be found that a slight cloudiness occurs here also after a few seconds, so that the neutral point is reached and the titration is ended. If we have used up to this point about 12.8 cc. of the chloride of barium solution, the 100 cc. of urine contains 0.128 gm. of  $\text{SO}_3$ , from which the amount in twenty-four hours can be very easily reckoned. But if by an incautious addition of the chloride of barium solution the point has been far exceeded in the first experiment, a few cc. of the exactly equivalent sulphate of potassium solution are added, and the boundary is determined by a more careful addition of the baric chloride solution. The number of cc. of the sulphate of potassium solution added must naturally be subtracted from the whole number of cc. of the baric chloride solution used, when making the calculation.

Although the operation appears long it can be performed in half an hour very easily and gives satisfactory results. 100 cc. of urine contained 0.129 gm. of  $\text{SO}_3$  as determined by weighing, and by titration to the neutral point it was estimated to contain 0.128 gm. 100 cc. of another urine gave 0.139 gm.  $\text{SO}_3$ , determined by weighing, and 0.137 gm.  $\text{SO}_3$  by titration. (Analytical Experiments.)

*Gravimetric Determination.*

100 cc. of filtered urine are measured off with a pipette, it is allowed to flow into a small beaker, heated on the water bath, a little hydrochloric acid added, and then chloride of barium solution in slight excess. The sulphate of barium formed will

settle very quickly and the supernatant fluid will become clear. The whole precipitate is collected on a small filter, the weight of whose ash is known, it is then washed with hot water until the wash water is no longer made cloudy by sulphuric acid, and dried as soon as the washing is finished. The sulphate of barium obtained must then be ignited; it is, therefore, transferred from the filter to a small weighed platinum crucible. After the filter has been ignited on the cover of the crucible, the cover is placed on the latter, taking care, however, that the ash does not come in contact with the precipitate, and it is ignited strongly for a short time. But since organic matters are always precipitated from the urine with the sulphate of barium, a little sulphide of barium is formed on heating; therefore after the crucible has become cold again its contents must be moistened with a few drops of dilute sulphuric acid and be heated once more until the excess of sulphuric acid is expelled. The crucible is then allowed to cool in a desiccator over sulphuric acid and is afterward weighed. If the weight of the crucible and of the filter ash are subtracted from the total weight, we obtain as the difference the amount of sulphate of barium precipitated, from which it is easy to calculate the sulphuric acid, since 100 parts of sulphate of barium correspond to 34.33 parts of sulphuric acid.

## § 70.

### 1. ESTIMATION OF SUGAR BY FEHLING'S METHOD.

*A. Principle.* The method of estimating sugar in the urine is founded on its property, mentioned in § 25, D, 7, of precipitating the copper in the form of red cupreous oxide from alkaline solutions of sulphate of copper. If a copper solution of known strength is used, a fixed volume of which is exactly reduced by a certain amount of grape sugar, we can easily accurately estimate the sugar contained in solutions of unknown strength, if we determine the volume which is just sufficient to completely decompose a measured amount of the standard copper solution. 180 parts by weight of grape sugar (=1 equivalent) precipitate the copper from 1247.5 parts by weight of cupric sulphate (=10 equivalents).

*B. Preparation of the Copper Solution.*

34.639 gm. of pure crystallized sulphate of copper are dissolved in about 200 gm. of water; on the other hand 173 gm. of crystallized chemically pure potassio-sodic tartrate are dissolved in 500 or 600 gm. of sodic hydrate of specific gravity 1.12, and the sulphate of copper solution is gradually added to this alkaline solution. The clear mixed fluid is then diluted to one liter. 10 cc. of this copper solution are exactly reduced by 0.05 gm. of grape sugar. If the copper solution is to be kept for a long time, it is absolutely necessary to place it in small bottles (40 to 80 gm.), which are to be closed with good stoppers, sealed, and then stored in a cool place.

*C. Performance.*

In order to obtain favorable results by this method it is a necessary requisite that the urine to be tested for sugar as well as the copper solution shall be largely diluted. It is well to treat 10 cc. of the copper solution with 40 cc. of distilled water, and to dilute 10 or 20 cc. of the urine, which has been previously filtered, to ten or twenty times its own volume, so that at most it contains  $\frac{1}{2}$  per cent. of sugar.

Then after heating the measured and diluted 10 cc. of the standard copper solution in a small flask over a lamp nearly to the boiling point, the urine also diluted is added from a burette, at last drop by drop, until complete reduction has taken place, that is, until the fluid has become colorless. In doing this, however, there are many things to be heeded. As soon as the first drops of the saccharine fluid fall into the hot copper solution, the separation of suboxide commences. The mixture appears reddish brown with a greenish tinge on account of the suspension of the red cupreous oxide in the blue solution; the greater the addition of the solution of sugar, however, the richer and redder the precipitate becomes, and it is not until the latter has assumed a deep red color and the fluid has become perfectly colorless that the experiment can be regarded as finished.

The analysis is performed most accurately and quickly as follows: As soon as the mixture in the flask, on very gentle boiling, and after the repeated addition of the diluted urine, commences to assume a red color, the flask is removed from the flame and the separated cupreous oxide is allowed to settle, which occurs the more readily and quickly the nearer the



point of complete reduction of the cupric oxide is reached. The faintest trace of blue color may be observed with great sharpness, if the flask is brought between the eye and a window, and the fluid viewed by horizontal transmitted light. If we are still far from the end reaction, as remarked above, the cupreous oxide already separated deposits more slowly, but the blue color can still be seen very distinctly by transmitted light if the mixture is given a rotary motion while we look through it. Finally, the more nearly the blue disappears from the fluid, kept very near the boiling point always, the more carefully must we allow the sugar solution to run in; but at last a point appears after the repeated addition of the latter and continued heating, at which the last blue shimmer disappears with one or two drops of the sugar solution, and gives place to a very faint yellow tinge. The reaction is now finished, and all of the cupric oxide is reduced; nevertheless we can be certain by further tests. We, therefore, filter some of the boiling fluid into three test tubes; one specimen of the absolutely clear filtrate is acidulated with hydrochloric acid and tested with sulphuretted hydrogen water, while a second specimen, after acidulating with acetic acid, is treated with ferrocyanide of potassium. Neither of the two reagents should change the fluid; the first, therefore, must not color it black nor the second reddish brown or precipitate it at all. If the two behave indifferently we may conclude that all of the copper is reduced and precipitated, and that we have added a sufficient amount of the solution of sugar. It is well to take this into consideration, however, that the cupreous oxide very quickly oxidizes again and dissolves, therefore in testing the fluid it must be filtered off immediately after the end of the experiment, while boiling, since after it has cooled it will always have a bluish color on account of the cupric oxide which has been dissolved again.

If no more undecomposed cupric oxide is found by means of the above reagents, an error may nevertheless have been made by having added too much of the urine, so that naturally the amount of sugar will be calculated less than it really is. Therefore, the third specimen of the clear, almost colorless filtrate is treated with a few drops of copper solution and heated to gentle boiling. Even when only a trace of sugar has been



added in excess, after a short time there occurs a distinct red shimmer, which may be quite beautifully and readily appreciated by reflected light. When a great excess of sugar has been added the filtrate has a yellow color; then there is nothing to do but to perform the analysis over again more carefully, which indeed is always to be advised as a test of accuracy.

However, if the experiment is performed in a small flask in the manner described, as was first suggested by A. Ziegler, the right end point may be obtained with great accuracy with a little experience, as I have demonstrated.

The volume of urine used contains, therefore, as was mentioned above, 0.05 grm. of sugar. Now since the amount of sugar in the fluid is inversely proportional to the volume used, to determine the per cent. of sugar in the urine, we must divide five by the amount in cubic centimeters of urine used, if it was not diluted; but if, for example, it was diluted to twenty times its volume, we must divide  $20 \times 5 = 100$  by the number of cc. used.

Of the other constituents of urine it is probably the uric acid chiefly which is known to reduce the copper solution on boiling, and which may, therefore, influence the result. Fehling, for this reason, first precipitates the urine with basic acetate of lead. But Brücke disapproves of this precipitation, because, according to him, some of the sugar is precipitated at the same time. Pure fruit sugar produced from urine is, however, not precipitated by basic acetate of lead, and it can at most, therefore, only be carried down mechanically. Fehling experimented with normal urine to which from 10 to 12 per cent. of sugar was added. But if we have a diabetic urine of about 8 per cent., when 10 cc. of it are diluted to 200 cc., we require to decompose 10 cc. of Fehling's solution only 12.5 cc. of this diluted fluid corresponding to 0.6 cc. of the original urine. The uric acid contained in 0.6 cc. of diabetic urine would be a very small amount.

I have made several experiments with diabetic urine in order to convince myself of its action.

a. 10 cc. of urine were diluted to 200 cc. and directly used for analysis. In several trials 12.3 cc. were required.

b. 10 cc. of urine were diluted with 188 cc. of water and 2 cc. of basic acetate of lead, which were more than sufficient to pro-

duce complete precipitation, were added. After twelve hours it was filtered, and exactly 12.2 cc. were used to 10 cc. of the Fehling's solution.

c. 150 cc. of urine were left at rest for forty-eight hours at 5° or 6° C. with 5 cc. of hydrochloric acid of 1.1 specific gravity. 10.33 cc., corresponding to 10 cc. of the original urine, were filtered from the separated uric acid, diluted to 200 cc., and used for analysis. In several trials 12.3 cc. were required.

The same experiments were repeated several times with diabetic urine of other days without any variation in the result worthy of mention by the different methods. But apart from this consideration, in many cases a precipitation with basic acetate of lead may be desirable, and when this is done in a urine previously diluted to at most 0.5 per cent., the amount of sugar precipitated will be none, or, at least, very slight indeed, as was determined by Fehling's experiments. If albumen is present, it must be removed; the urine is heated to boiling after the addition of a drop of acetic acid, the coagulum which forms is filtered off, carefully washed, and the filtrate obtained, diluted if necessary, is used for determining the sugar.

## 2. ESTIMATION OF THE SUGAR BY KNAPP'S METHOD.\*

A. *Principle.* This method depends on the complete reduction of cyanide of mercury in alkaline solution to metallic mercury by means of grape sugar at a boiling temperature. 400 mgrm. of cyanide of mercury require 10 mgrm. of anhydrous grape sugar.

B. *Preparation of the Solution.* 10 grm. of pure dry cyanide of mercury are dissolved in water, 100 cc. of sodic hydrate of 1.145 sp. gr. are added, and the mixture is diluted to 1,000 cc.

C. *Performance.* The analysis is performed as with Fehling's solution. 40 cc. of the cyanide of mercury solution are brought to the boiling point in a flask, and the urinary fluid containing about  $\frac{1}{2}$  per cent. of sugar is allowed to flow in until all of the mercury is precipitated. In the mixture of urine used we have had just 100 mgrm. of grape sugar. When the sugar solution flows into the boiling alkaline solution of cyanide of mercury,

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\* Annalen d. Chem. u. Pharm., Band 157, p. 252.

the mixture immediately becomes turbid, but clears up toward the end of the operation and then assumes a yellow color. In order to follow the course of the operation, from time to time a drop of the mixture is put on a piece of the finest Swedish filter paper, which is placed over a small beaker containing a little of the strongest sulphide of ammonium. If a brown spot is no longer formed on the paper, the experiment is ended. The reaction is still more delicate when a drop is placed on a strip of Swedish paper, and then a drop of sulphide of ammonium on a glass rod is held over it for about half a minute. At first the whole spot becomes brown, but toward the end a light-brown ring only forms on its edge, which can finally be distinctly recognized only when the transparent spot is held up toward a bright light. The fresh transparent spot remains wholly unchanged by sulphide of ammonium vapor at last, so that with a little experience the titration can readily be carried within  $\frac{1}{10}$  cc. of the one-half per cent. solution. If the spot is allowed to dry finally, a clear-brown ring of sulphide of mercury always appears, since a neutral point seems to be formed, as there always remains in solution a trace both of grape sugar and of cyanide of mercury, which is removed only by an excess of the one or the other. We must, therefore, regard the color of the *fresh* spot as the standard. For greater accuracy a few cc. of the fluid are at last filtered off, acidulated with acetic acid, and tested with sulphuretted hydrogen to see whether mercury is present or not.

According to comparative investigations which my assistant, Mr. Pillitz, conducted with diabetic urine, Knapp's method gave results which coincided very well with Fehling's method. (Analytical Experiments.) The easy preparation of the solution of cyanide of mercury and its absolute durability are decided advantages.

### 3. ESTIMATION OF SUGAR BY CIRCUMPOLARIZATION.

#### a. *With the Ventzke-Soleil Polarizer.*

A. *The Polarizer.* Fig. 30 shows the Soleil-Ventzke saccharimeter *A* with the lamp which belongs with it.

We will first consider the optical arrangement and then the employment of this ingenious apparatus. The light coming

from the lamp *B* first falls on a large Nicol prism at *l*, which, with the quartz plate at *k* cut perpendicular to the axis, can be turned around the axis of vision by means of the cogwheels *m* and *p* and the iron rod *nm*. At *i* there is a second fixed Nicol prism, and in front of it at *h* the soleil double plate made of quartz rotating to the right and left. In the front part of the

FIG. 80.

apparatus there is at *g* a left-handed quartz plate cut perpendicular to the axis, and in front of it a compensator made of two right-handed quartz prisms, which prisms can be so shifted by means of a driving gear on the head, *o*, that the polarized light which traverses the apparatus has to pierce a thicker or thinner layer of right-handed quartz. At *d* there is again a Nicol prism which can be turned around the axis of vision by a small key at *e*, and lastly at the head of the instrument at *bc* there is a small telescope to enable every eye to distinctly see the double plate standing at *h*. Then the glass tube filled with the urine to be examined and closed at both ends with glass plates is inserted between *p* and *p*. The compensation prisms at *f* support above a scale and nonius, which are best so divided that the parts of the scale to the right of the 0-point directly give the per cent. of grape sugar in 100 cc. of urine, when the observation is made in a tube 200 mm. long at 17° C. On the left of the 0-point a second scale gives under the same circumstances the per cent. of albumen in 100 cc. of urine. If we

place the compensator at  $f$ , by means of the thumb-screw  $o$ , in such a manner that the 0-mark of the nonius exactly corresponds with that of the scale, the two right-handed quartz prisms have together the same thickness as the left-handed quartz plate at  $g$ , and the two neutralize each other, so that the eye looking at  $a$ , when the two Nicol prisms at  $d$  and  $i$  are properly placed, will see the double plate  $h$  having exactly the same color. The same is the case if the examining tube is filled with distilled water and inserted between  $pp$ . If the two quartz prisms are now shifted to the right or left by means of the screw  $o$ , the two halves of the double plate  $h$  immediately appear unequally colored, just so if the compensator stands exactly on 0 and the examining tube contains a fluid rotating to the right or left. If, for example, this is filled with diabetic urine, the compensator must now be turned toward the right in order to restore again the deranged equality of color of the double plate. Lastly, it is of great importance to be able to give the double plate any shade of color desirable, since all eyes do not possess a like sensitiveness for all colors. For this purpose the back part of the apparatus situated next the lamp is of service. By means of the rod  $nm$  and the cogwheels  $m$  and  $p$  the quartz plate at  $k$  and the Nicol prism  $l$  can be turned around the axis of vision; the former, therefore, since it is between a fixed Nicol prism,  $i$ , and a movable one,  $l$ , will run through all shades of color, and also allow only colored light to pierce the apparatus, by which the original color of the double plate may be varied at pleasure.

*Proper Arrangement of the Apparatus.* First, the saccharimeter is so placed, as represented in fig. 30, that the brightest part of the illuminating lamp  $B$  sends the light through the lateral connecting tube  $r$  of the clay cylinder  $s$ , which has its outer surface blackened, directly in the axis of the apparatus; then the observation tube, which has been exactly filled with distilled water, is placed between  $pp$ , and the compensator is so arranged that the 0-point of the nonius coincides with the zero-point of the upper scale. If we now observe at  $a$ , by shortening or lengthening the telescope  $bc$  we soon reach the point at which the picture appears clear and well defined and the fine line which divides the double plate into halves becomes sharply defined. If the double plate appears absolutely isochromatic

and if the isochromatism also remains in all the shades of color which we can give it by turning the rod  $nm$ , then the apparatus is in order; in the other case the zero-point must be corrected. For this purpose everything is left unchanged except the Nicol prism at  $d$ , which is turned with the key at  $e$  a little to one side or the other, until the desired color of the two halves of the double plate has been attained. As a correction the scale is moved a little one way or the other by turning the screw  $o$  until the picture appears exactly isochromatic again. If we look at the scale and nonius now, the two zero-points must exactly coincide; in the contrary case a new adjustment must be made of the Nicol prism  $d$ . This correction, however, is only very rarely necessary; if the instrument is carefully kept the zero-point remains constant for years.

B. *Process of Estimating Sugar.* Diabetic urine can usually be directly examined in the polarizer if it is filtered so as to be absolutely clear. When the apparatus has been given the position shown in the figure, the 200 mm. long observation tube is filled with clear filtered urine, or urine which has been decolorized by animal charcoal if necessary, taking care, however, to avoid inclosing air-bubbles, and it is then laid between the points  $p$  and  $p$  in the apparatus. Then after the telescope has been sharply focused, the compensator is turned until the two halves of the double plate appear nearly isochromatic, and those shades of color are sought, by turning the Nicol prism at  $l$  to the right or left with the rod  $nm$ , in which the slightest difference in the color of the two halves of the double plate is most distinctly perceptible. A pale rose will meet this purpose best; at all events, we may soon convince ourselves that all dark, fervid colors which the double plate gradually assumes on turning the rod  $nm$  are wholly unserviceable. Frequent practice of the eye will soon enable us to hit upon the right one. We can now proceed to an accurate adjustment of the picture, isochromatism of the two halves. The screw  $o$  is, therefore, seized, and the compensator moved back and forth until complete isochromatism of both halves is attained. The principal rule in this procedure is never to observe longer than ten seconds at a time.\*

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\* The two glass plates which close the observation tube must not be pressed on too closely, since they may themselves easily give rise to double refraction and show colors with polarized light, which cause the rotation produced by the

Since the eye quickly habituates itself to nice differences of color, an accurate result can never be arrived at by a single adjustment and too long an observation.

When at last, after several observations, we think that the two halves of the picture are isochromatic, we again turn the prism at  $l$  with the rod  $nm$ ; if the two halves of the plate remain absolutely isochromatic in all the shades of color which the double plate now produces, then the experiment is finished; in the other case the compensator must be more accurately adjusted until at last the object aimed at is attained. The scale and nonius are now read off. The zero-point of the latter has removed considerably toward the right from the zero-point of the scale; if it coincides with a mark of the latter, it shows with the observation tube 200 mm. long as many per cent. of sugar in 100 cc. of urine as there are divisions from the zero-point of the scale to the zero-point of the nonius, since every line of the scale corresponds to 1 per cent. of sugar. If, however, the zero-point of the nonius lies between two divisions of the scale, we must seek a line of the scale of the nonius lying to the right which coincides with a line of the scale. When this is found, we count the divisions from the zero-point of the nonius to the one which coincides with the division of the scale inclusive. Each division on the nonius indicates  $\frac{1}{10}$  per cent. of sugar. The whole per cents., therefore, are read off on the scale; the tenths are read off on the nonius, for which a lens may be used with advantage. If the urine is too dark, the estimation is undertaken in an observation tube only 100 mm. long; if it succeeds we have only to remember that every division of the scale indicates 2 per cent. and every division of the nonius  $\frac{2}{10}$  per cent. of sugar. But if we do not attain our object in this way we must decolorize the urine by means of animal charcoal, or a measured volume of the urine is precipitated with a known volume of sugar of lead solution, filtered, and the clear colorless filtrate is examined. Of course the dilution caused by the solution of lead is to be taken into account in the estimation.

C. *The Urine also contains Albumen.* If albumen is present

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urine which is to be examined, to appear more or less erroneous. (*Zeitschrift f. analyt. Chemie*, Band 8, p. 211.)



at the same time with sugar, it must be removed first, since, the reverse of sugar, it turns the plane of polarization to the left. The albumen in 100 cc. of urine is coagulated by heating in a flask after carefully adding a little acetic acid, the fluid is filtered into a graduate and washed with water until the filtrate amounts to exactly 100 cc. again. After it has cooled it is examined with the polarizer.

According to the comparative experiments of Tscherinoff\* and my own considerable experience, there is no doubt that the figures obtained with the Ventzke-Soleil apparatus in diabetic urine often vary considerably from the chemical determinations. The difference may be either minus or plus. In the first case we must consider that the urine contains another reducing substance, but one which does not turn the plane of polarization, whether it is sugar optically inactive or some other substance, or that besides the ordinary grape sugar, which turns to the right, there is also a small amount of sugar or some other body which turns the plane to the left. In cases where only plus is the result, in my experience the rarer ones, we may assume that the diabetic sugar possesses, at least in part, a higher rotatory power than the ordinary grape sugar, or that another body is present which turns to the right but does not have a reducing action. (Analytical Experiments.)

b. *With the Polaristrobometer of Wild.*

Figs. 31 and 32 show Wild's polaristrobometer and the lamp which belongs with it. The brass column, *F*, stands on an iron tripod, *E*, and bears on its upper end the horizontally and vertically movable support, on one end of which is the polariscope, *A*, and on the other end the circular disk, *K*, with the Nicol-setting. The polariscope consists of a feebly magnifying telescope focused on infinity, before whose objective a double plate of calc-spar is placed, while in the focus of the objective there is a diaphragm with cross-hairs. The double plate, according to the theory of Savart's polariscope, is made of two 3 mm. thick plates of calc-spar cut at 45° to the optical axis, and with their principal planes crossing at right angles. At the other end of the polariscope the analyzing Nicol prism is so inserted that its principal plane stands horizontally, and includes with

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\* Zeitschrift f. analyt. Chem., Band 6, p. 502.



that of the double plate an angle of  $45^\circ$ . A screen, *M*, at the ocular, serves to keep off the disturbing side light from the eye of the observer.

Finally, the polarizing Nicol is inserted in a shell, *N*, at the circle, *K*, and on its mounting is afterward placed the dark tube *D*.

The circular disk and Nicol may be turned by the knob, *C*, by means of a toothed pinion. The index, *I*, for reading off the

FIG. 81.



position of the circular disk is put on the support of the latter and has a simple mark. The telescope, *P*, serves for reading off its position, and its ocular, *B*, lies immediately beside the ocular, *A*, of the polariscope. The division is lighted by a movable perforated mirror, *S*, at the objective end of this telescope, and a candle or gas flame at the proper height serves as the source of light.

One half of the circle contains a division marked with grams, which extends from the zero-point to about 300 toward the right and 150 toward the left. Each interval of this division corresponds to 1 gm. of pure cane sugar, which is contained

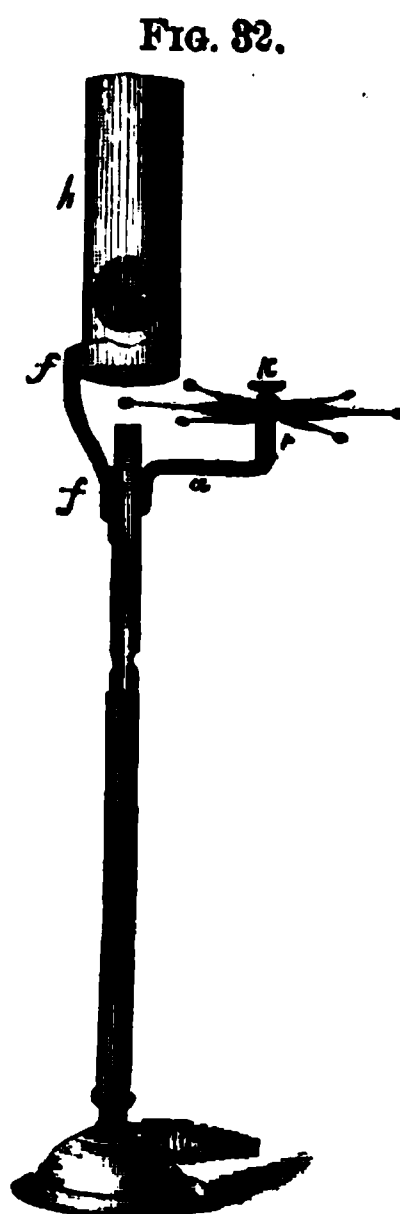
in 1,000 cc. of solution, and when a tube 200 mm. long is used. On the opposite half of the circle, on the contrary, there is a second division into degrees and  $\frac{1}{4}$  of a degree (entire circumference  $360^\circ$ ), which serves to express the angle of rotation of the plane of polarization by any desired substances in an independent manner.\*

Lastly, a special bed serves to receive the observation tube between the circular disk and the polariscope.

The gram division mentioned depends on the use of a homogeneous source of light, and, indeed, a yellow light of the refrangibility of the line *D*. Fig. 32 shows the Bunsen gas-lamp, which serves to produce this light.

On the side arm, *a*, there is a small movable wheel, *r*, on whose spokes small glass tubes with platinum wire fused into them can be fastened. These wires contain beads of chloride of sodium, which are turned into the front edge of the flame by means of the knob, *k*, and immediately produce a clear homogeneous yellow light. The chimney, *h*, rests on the movable support, *f*, and ensures as steady a flame as possible. The lamp is so placed that the round opening, *c*, in the chimney, stands exactly in front of the opening, *D*, so that the field is illuminated perfectly symmetrically. In order to obtain the best possible results and at the same time to tire the eye least, it is well to place the apparatus in a dark room and carefully avoid every disturbing side light.

When we have a sufficiently bright and perfectly homogeneous light, about the mark 300 of the division, marking in grams, is brought into the field of the telescope, *P*, by turning the




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\* The mechanics, Hermann and Pfister, in Bern, who furnish Wild's Polaristrobometer of excellent finish at a price of about 800 marks (\$75), have lately made instruments in which the circle is divided throughout in  $\frac{1}{4}$  degrees ( $900^\circ$ ), so that it is possible to read off the angle of rotation in all four quadrants.

knob, *C*, and on looking through the polariscope, *A*, a bright-yellow field is obtained, which is traversed by horizontal black

Fig. 33, *c* and *b*. lines, and shows also the cross-hairs (fig. 33, *a*). If the latter do not appear sharply defined, the ocular of the telescope, *A*, is drawn out more or less, until they become so; and now the horizontal black fringe will be most distinctly seen also.

If we now turn the knob, *C*, again (in the direction of the arrow) the horizontal lines gradually become paler and at last wholly disappear. This point in Wild's apparatus shows that the instrument is adjusted, just as in Soleil's saccharimeter the same color of the two quartz halves indicates the same thing.

If the instrument is accurately adjusted, when the lines completely disappear, the index mark exactly corresponds with the zero-point of the circle division. If a slight deviation should appear here, its amount may either be taken into account by addition or subtraction in later measurements, or with the aid of the two correction-screws, at *G*, the polariscope may be turned in its sheath, *L*, micrometrically to the left, until the horizontal lines completely disappear, while the index line remains at zero. (Fig. 33, *b*.)

*Procedure in Estimating.* According as the color of the perfectly clear filtered urine is lighter or darker, the observing tube 100 or 200 mm. long is chosen for the estimation. We first bring the circle division, which is furnished with numbers running from 0 to 100 and divided into  $\frac{1}{2}$  degrees, into the field of the telescope, and adjust it exactly at the disappearance of the fringe, when about the division 50 will coincide with the index. Reading off the position is accomplished by estimating the tenth of a division at  $\frac{1}{10}^{\circ}$ , when by multiplying by two the  $\frac{1}{10}^{\circ}$  and the  $\frac{1}{10}^{\circ}$  are changed to  $\frac{1}{5}^{\circ}$  and  $\frac{1}{55}^{\circ}$ , so that we can write them as decimals.

After the starting-point has been determined the tube filled with urine is placed on the apparatus and we turn toward the increasing numbers until the fringes disappear again. If the first reading is subtracted from the new one, we obtain the angle of rotation  $\alpha$ , from which the amount of sugar *C*, that is,

the weight of diabetic sugar present in a liter, is given in grams by means of the formula

$$C = 1773 \frac{\alpha}{L}$$

in which 1773 is the constant rotation of diabetic sugar according to Hoppe-Seyler's most recent determinations,\* L the length of the tube in millimeters, and  $\alpha$  represents the angle of rotation observed.

The following table gives the results of these calculations for whole degrees and tubes 100 and 200 mm. long:

ANGLE OF DEVIATION.	100 MM.	200 MM.
1°	17.73	8.865
2°	35.46	17.730
3°	53.19	26.595
4°	70.92	35.460
5°	88.65	44.325
6°	106.38	53.190
7°	124.11	62.055
8°	141.84	70.920
9°	159.57	79.785
10°	177.30	88.650

### Example:

When the tube is empty or removed, we have found 50° as the point of departure. After filling the tube 100 mm. long with urine the adjustment with homogeneous sodium light gave 53.61°; the angle of rotation, therefore, is 3.61°, and from it we can reckon for the observation tube 100 mm. long according to the above table:

As concentration for 3°, . . . . . 53.190 gm.

As  $\frac{1}{10}$  of the concentration for 6°, . . . . . 10.638 “

As  $\frac{1}{100}$  of the concentration for 1°, . . . . . 0.177 “

Amount, . . . . . 64.005 gm.

† Zeitschrift f. analyt. Chem., Band 14, Heft 8.

In one liter of urine, therefore, there are contained 64.005 gm. of diabetic sugar.

#### 4. ESTIMATION OF SUGAR BY FERMENTATION.

*A. Principle.* From § 25, D, 8, we know that diabetic sugar mixed with yeast undergoes vinous fermentation. One equivalent of diabetic sugar thereby decomposes into 2 equivalents of alcohol and 4 equivalents of carbonic acid; if we estimate the carbonic acid formed by the fermentation of a fixed amount of diabetic urine, we can calculate from it the quantity of sugar present. 100 parts of carbonic acid correspond to 204.54 parts of sugar.

*B. Performance.* In carrying out the test we use the apparatus represented in fig. 34. 20 or 30 cc. of urine are placed in the small flask A, a little well-washed so-called dry yeast and a small amount of tartaric acid are added, and it is connected by means of the bent tube *c* with the small flask B, which is half filled with concentrated sulphuric acid. The tube *a* of the small flask A is closed at the top by a little ball of wax, *b*, and the apparatus is then weighed. It is next exposed to a temperature of about 30° or 40° C., when fermentation with the evolution of carbonic acid will commence directly. The bubbles of gas pass through the tube *c* and the sulphuric acid in the flask B, and then escape perfectly dry through the tube *d*, which should be connected

FIG. 34.

with a small U-shaped chloride of calcium tube, so as to prevent the access of atmospheric moisture to the concentrated sulphuric acid in B.

In most cases the fermentation is completed in two or three days, the evolution of carbonic acid then ceases, and all of the sugar is decomposed. Then after gently warming the flask A to remove the carbonic acid which is still retained, a little air is drawn through the apparatus at the tube *a* until there is no longer any taste of carbonic acid, and it is then weighed again. The loss of weight gives us directly the amount

of carbonic acid formed by the decomposition, and from this we can easily calculate the corresponding amount of sugar, since 48.89 parts of carbonic acid correspond to exactly 100 parts of diabetic sugar.

If the urine contains albumen it must be coagulated by boiling, since otherwise decomposition may readily occur, which, as is well known, is accompanied by the evolution of gas. By the addition of tartaric acid, according to Lehmann, other decompositions are prevented, while at the same time the vinous fermentation is promoted.

From the experiments of Pasteur there is no longer any doubt that in the fermentation of sugar, not only carbonic acid and alcohol, but also other substances, amyl alcohol, butyl alcohol, etc., and even succinic acid and glycerine, may be formed, so that the carbonic acid is not a perfectly accurate measure of the sugar; this may be the reason why many chemists have always found less sugar in diabetic urine by the fermentation test than by the excellent method of Fehling. I unconditionally prefer Fehling's method.

##### 5. QUANTITATIVE ESTIMATION OF SUGAR FROM THE DIFFERENCE IN SPECIFIC GRAVITY BEFORE AND AFTER FERMENTATION.

The method proposed by Roberts, in the year 1861, of estimating the sugar in the urine from the difference in specific gravity before and after fermentation, has recently been subjected to a rigid test by Manassein,\* who has established the usefulness of the procedure beyond all doubt.

After the specific gravity of the original urine has been determined by the picnometer or a delicate Mohr balance, with careful consideration of temperature, it is treated with pure washed yeast and left to ferment in a sufficiently large flask, best at a temperature of from 20° to 24° C. At the temperature above given the fermentation is usually ended in twenty-four hours; the fluid now becomes clear and the yeast settles to the bottom. When this point is reached it is filtered, and the specific gravity of the clear fluid is once more determined with the picnometer or the Mohr balance.

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\* Centralblatt f. d. med. Wissenschaft., 1872, p. 551.

For a difference of 0.001 in the specific gravity before and after fermentation we reckon 0.219 per cent. of sugar. If a urine before fermentation, therefore, had a specific gravity of 1.0298, and after it one of 1.0055, the amount of sugar would be calculated for the difference of 0.0243 at

$$\frac{0.0243 \times 0.219}{0.001} = 5.32 \text{ per cent.}$$

Or the difference of the specific gravities is multiplied by 1000 and divided by the factor 4.56, which would be obtained by multiplying the difference of the specific gravities by 1000 and dividing this product by the per cent. of sugar found with the polarizer. According to this the amount of sugar for a difference in the specific gravities of 0.0243 is reckoned at

$$\frac{0.0243 \times 1000}{4.56} = 5.33 \text{ per cent.}$$

From a number of estimates which I have made the above method is by no means inferior in point of accuracy to others. That it requires at least twenty-four hours time and that yeast is not always at hand in the laboratory are disadvantages which it has in common with the methods hitherto used for estimating the sugar by fermentation.

## § 71.

### 1. ESTIMATION OF IODINE BY THE METHOD OF KERSTING.\*

*A. Principle.* The method of estimating iodine depends simply on the fact that all of the iodine is separated from even a tolerably dilute solution of a metallic iodide by distillation with sulphuric acid, so that no more traces of iodine can be detected in the residue if the distillation is continued sufficiently long. The iodine is estimated in the distillate by a standard solution of chloride of palladium. If a solution of a metallic iodide is mixed with an excess of a solution of the chloride of palladium and a little hydrochloric acid at from 60° to 100°, the iodide of palladium formed separates on shaking after a few seconds in black caseous flakes and the supernatant fluid appears perfectly clear and colorless. If, on the other

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\* *Annal. d. Chem. u. Pharm.*, Band 87, p. 21.

hand, the iodide solution is present in excess, the precipitation takes place much more slowly and the palladium iodide deposits partly on the sides of the glass as a black coating. For these reasons, therefore, in the estimation of iodine we do not add the solution of palladium to that of the iodine, but we measure off a fixed volume of the latter and determine the amount of the fluid to be tested for iodine which is just sufficient to precipitate a definite amount of palladium solution. Since the mixture becomes almost absolutely clear on heating and shaking, and since in the second place  $\frac{1}{30}$  to  $\frac{1}{300}$  mgrm. of iodine may be detected by palladium, and conversely  $\frac{1}{100000}$  mgrm. of palladium may be distinctly recognized by means of iodine by the occurrence of a brown color, the estimations appear to be very accurate according to my own experiments performed with pure solutions of iodide of potassium and palladium chloride, both of known strength.

### B. *Preparation of the Solutions.*

#### 1. *Standard Solution of Iodide of Potassium.*

The solution of iodide of potassium must contain exactly  $\frac{1}{1000}$  of iodine, and is, therefore, readily obtained by weighing off 1.308 gm. of pure ignited iodide of potassium, free from iodate of potassium, dissolving and diluting it to a liter. 1 cc. of this solution contains then 1 mgrm. of iodine, since 1.308 gm. of iodide of potassium exactly correspond to 1 gm. of iodine ( $127:166.11=1:x=1.308$ ).

This solution of iodine is used for standardizing the solution of chloride of palladium.

#### 2. *Acid Solution of Chloride of Palladium.*

##### a. *Dissolving the Palladium.*

The palladium solution is prepared from the metal. For example, 1 gm. is weighed off, dissolved in hot aqua regia, evaporated to dryness at  $100^{\circ}$ , then fifty parts of concentrated hydrochloric acid are added and diluted with water to 2,000 cc. Since, however, commercial palladium is probably seldom pure, the true strength of this solution must be ascertained, for which purpose the iodide of potassium solution 1 may be used, which contains  $\frac{1}{1000}$  of iodine.

##### b. *Titration of the Palladium Solution.*

10 cc. of the palladium solution to be tested are put into a small flask of about 100 or 200 cc. capacity, the glass is stop-



pered, and heated on the water bath to 60° or 100°. The iodine solution 1 is now gradually added from a pipette or burette, it is vigorously shaken and heated a few seconds. A small amount of the fluid, which becomes clear in a few minutes, is poured into two small, narrow test tubes, so that both contain about one or two inches of fluid. A few drops of the iodine solution are then added to one tube and compared with the other to see whether a brown color is produced or not. If the former is the case, the specimens are washed into the original fluid, more iodine solution is added, it is shaken, heated, again tested in the manner indicated, and the process continued until a new amount of iodine produces no further color. When this point is attained a little fluid is filtered off, and if it is not perceptibly browned either by palladium or by the iodine solution, it can contain scarcely  $\frac{1}{100000}$  of an excess of these substances. Although this process appears difficult and tedious, it may be easily and accurately performed in at most ten minutes. We calculate the amount of palladium in the solution of palladium chloride from the number of cc. of the iodine solution used.

1 cc. of the iodine solution contains 1 mgrm. of iodine, and this corresponds to 0.42 mgrm. of palladium ( $127:53.3=1:x=0.42$ ).

For example, if we have used 11.9 cc. of the iodine solution to precipitate 10 cc. of the palladium solution, they correspond, since they contain exactly 11.9 mgrm. of iodine, to  $11.9 \times 0.42$  mgrm. of palladium. 10 cc. of the palladium solution contain, therefore, 4.998 mgrm. of palladium, and require of an iodine solution of unknown strength a volume in which exactly 11.9 mgrm. of iodine are contained, from which the amount of iodine in the whole fluid may be readily calculated.

### C. *Performance of the Analysis with Urine.*

In order to determine the amount of iodine present in urine which contains it, it is first necessary to separate it by distilling with sulphuric acid. The distilling apparatus represented in fig. 35 may be used for this purpose: *a* is a flask of about 300 cc. capacity, it is connected by a bent glass tube with the Liebig's condenser, *cc*, in which the vapors are condensed, and the distillate is collected in the small glass *d*, which serves as a receiver. If the quantity of iodine in the urine is at all considerable, 50 or 100 cc. are measured off with a pipette into the

flask *a*, which is placed in cold water, and then, while carefully avoiding too great a heat, 20 cc. of concentrated chemically pure (particularly that which is free from iodine) sulphuric acid is added drop by drop.

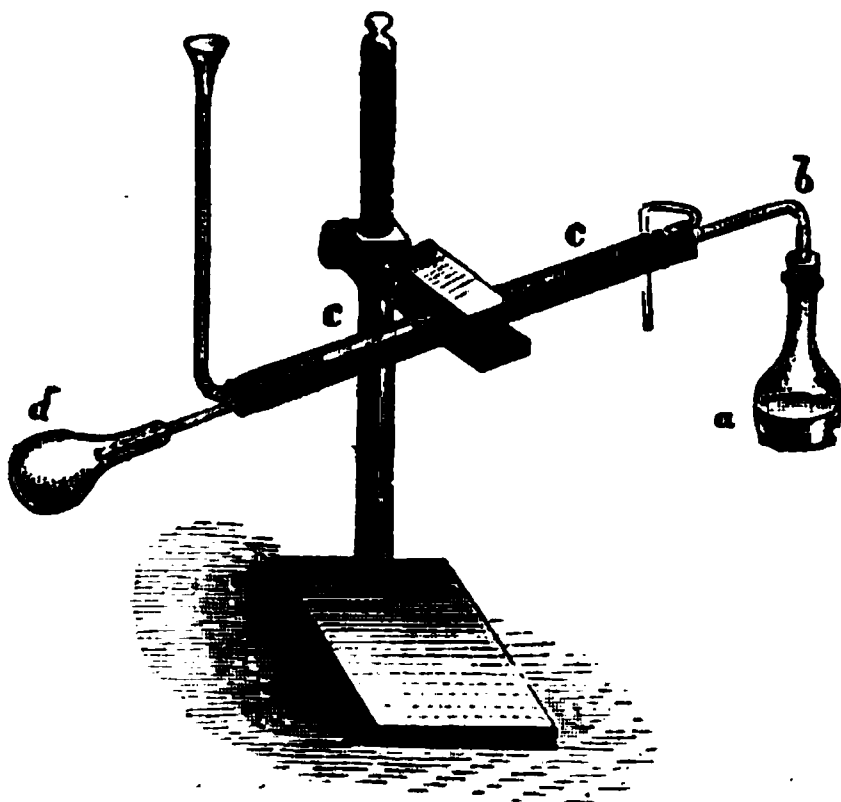
The flask is then connected with the condenser and the fluid is distilled until white fumes of sulphuric acid appear in the neck. If the urine contains but little iodine, however, a measured amount, about 200 or 250 cc., is supersaturated with liquor potassii, and distilled until from 20 to 40 cc. remain. This distillate contains no iodine. Observing the pre-

caution given above, 20 cc. of concentrated sulphuric acid are then poured on to the cooled residue in the flask, and the distillation is completed as before, that is, until the sulphuric acid begins to vaporize.

The distillate thus obtained in both cases contains hydriodic acid, all of the volatile acids of the urine, carbonic acid, sulphurous and sulphuric acids. Before it can be used for estimating the iodine, the sulphurous acid must be oxidized and removed. This is readily accomplished as follows: The distillate obtained is treated with one or two drops of starch paste (one part of starch,  $\frac{1}{10}$  of sulphuric acid, and twenty-four parts of water), then a saturated solution of calcic hypochlorite is dropped into it until the fluid just begins to become blue, and the blue color is again driven away by one or two drops of weak sulphurous acid water. The distillate is now ready for estimating the iodine; after the whole volume has been determined, which, therefore, corresponds to the amount of urine taken, it is poured into a Mohr's pipette, exactly 10 cc. of the standard solution of palladium are measured off, put into a glass, heated on the water bath, the urine-distillate containing iodine is then added, and the analysis performed exactly as before, according to B, 2, b.

If, for example, we have obtained 96 cc. of distillate from

FIG. 85.



100 cc. of urine, and have used 12 cc. of it to completely precipitate the 10 cc. of palladium solution which contains 4.998 mgrm., these 12 cc. contain 11.9 mgrm. of iodine ( $53.3 : 127 = 4.998 : x$ ). (See B, 2, b.)

In the 96 cc. of distillate, therefore, corresponding to 100 cc. of urine, there are  $8 \times 11.9 = 95.2$  mgrm. of iodine (0.0952 gm.).

## 2. HILGER'S METHOD.

While Kersting always obtained excellent results with the method described, Hilger\* states that according to his experiments Kersting's method constantly yields too small results. Hilger, therefore, recommends the following as the simplest method for estimating iodine quantitatively:

10 or 20 cc. of the palladium solution, according to the amount of iodine present in the urine to be tested, which is easily approximately determined by a qualitative test for iodine, are heated on the water bath in a glass vessel with a ground-glass stopper, and the urine containing iodine, first acidulated with hydrochloric acid and brought to a fixed volume, is added until all of the palladium is separated as iodide. The separation is very much hastened by violently shaking the mixture. Small amounts filtered off from time to time and treated with a few drops of the urine, on being heated indicate by becoming cloudy or remaining clear whether the reaction is finished or not. According to Hilger's observations the end of the reaction coincides with the moment at which the separation of the iodide of palladium in distinct flocculi commences, when the fluid is kept constantly boiling.

According to numerous experiments carried out by Hilger, the urine to be examined can, therefore, be directly used for estimating the iodine after it has been previously acidulated with hydrochloric acid. He also states that the removal of sulphuric acid, phosphoric acid, and other constituents of the urine is not necessary before performing the analysis.

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\* *Zeitschrift f. analyt. Chem.*, Band 12, p. 342, u. Band 18, p. 475.

### 3. COLORIMETRIC ESTIMATION OF IODINE BY THE METHOD OF H. STRUVE.\*

**A. Principle.** If a solution of iodide of potassium of known strength is prepared, and equal amounts of bisulphide of carbon are added to different quantities of the solution, and then a few drops of red fuming nitric acid are added, it is well known that all of the iodine is set free, and, after shaking, is taken up by the bisulphide of carbon. A scale of colored fluids containing known amounts of iodine is thus obtained, with which the shades of color obtained in the estimation of iodine in the urine are compared.

**B. Preparation of the Color Scale.** Struve used a solution of 1 gm. of iodide of potassium in 1,000 cc. of water: 1 cc. of it, therefore, contains 0.001 gm. KI or 0.00076 gm. of iodine. The burette used was such that 21 drops from it corresponded to 1 cc. 5 cc. of bisulphide of carbon are used with each test. If, then, the iodine is set free by a few drops of fuming nitric acid, and by shaking transferred to the bisulphide of carbon, the acid is removed by decanting with distilled water, and we thus obtain under a layer of pure water equal quantities of bisulphide of carbon, which are colored by different but definite quantities of iodine. All of these normal solutions, under a thin layer of water, are then sealed in glass tubes of pure white glass, which have a length of 15 cm. and an internal diameter of 8 mm. If the tubes are absolutely clean, more especially if they are free from organic matters, they retain the different shades of color for a long time without marked change if they are protected from direct sunlight and if the tubes are preserved in a cool, dark place.

In estimating iodine in the urine, the colored bisulphide of carbon which results is poured into a tube, which has the same dimensions as those containing the normal solutions, and the color is compared with the scale, which is best accomplished on a background of white paper with reflected light.

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\* Journ. f. pr. Chem., Band 105, p. 429. Zeitschrift f. analyt. Chem., Band 8, p. 280.

Struve used the following scale :

NUMBER OF DROPS OF THE NORMAL KI SOLUTION.	IODIDE OF POTASSIUM.	IODINE.
1	0·000048	0·000036
2	0·000096	0·000072
3	0·000144	0·000108
4	0·000192	0·000144
6	0·000288	0·000216
8	0·000384	0·000288
10	0·000480	0·000360
12	0·000576	0·000432
14	0·000672	0·000504
18	0·000864	0·000648
21	0·001000	0·000756
30	0·001440	0·001080

*C. Performance.* 20 cc. of water as cold as possible are poured into a pyriform flask of 50 cc. capacity and provided with a tightly fitting glass stopper; 1 cc. of the urine to be examined is then added, and afterward 5 cc. of bisulphide of carbon. The contents is gently shaken, and then a few drops of fuming nitric acid are added to the mixture from a small pipette. If it is now shaken and then left at rest, the bisulphide of carbon quickly collects on the bottom. The stopper is carefully raised, the glass filled with water as cold as possible, it is shaken, allowed to settle, and the acid water drawn off with a small siphon. The bisulphide of carbon is thus washed two or three times with water, when the colored bisulphide of carbon may be poured into a small previously-prepared glass tube for the comparison. But, if it has been necessary to use a large quantity of urine for the experiment, for example, 10 or 100 cc., it must first be evaporated nearly to dryness on the water bath after the addition of potassic hydrate, a concentrated solution of chloride of ammonium must be added to the dark-brown residue, and the whole heated until the fluid has a neutral reaction and no longer smells of am-

monia. When this point is reached, the cooled fluid is put into a flask, and the separation and estimation of the iodine carried out as indicated above. If, however, the bisulphide of carbon should not separate as a coherent mass, which indeed would scarcely happen, it is only necessary to evaporate the fixed volume of urine to dryness on the water bath, after adding the potassic hydrate, ignite the residue, extract with water, and test the filtered solution thus obtained, as recommended above, after it has been neutralized by boiling with chloride of ammonium.

## § 72. ESTIMATION OF IRON.

*A. Principle.* If a solution of permanganate of potassium is added to the solution of a ferrous salt which contains an excess of hydrochloric acid, the ferrous oxide becomes oxidized, and the permanganate of potassium, on the other hand, is reduced to manganous chloride. One equivalent of permanganate of potassium ( $\text{KO}, \text{Mn}, \text{O}_7$ ) yields five equivalents of oxygen, and thereby converts ten equivalents of ferrous oxide to ferric. If now the strength of the permanganate of potassium solution is known, an unknown amount of iron, which, of course, must be in solution as ferrous oxide, can be easily determined by ascertaining the volume which is just sufficient to complete the oxidation. The end point of the experiment is very beautifully and distinctly shown, by the bright-red color which is imparted to the whole fluid by the first drop of permanganate of potassium solution in excess.

### *B. Preparation of the Solutions.*

#### *1. Solution of Permanganate of Potassium.*

This is prepared by dissolving chemically pure permanganate of potassium in distilled water.

The strength of the permanganate of potassium solution must be determined anew before each series of experiments, since it gradually changes even with the most careful preservation. This estimation is performed in the most simple manner with a solution of ferrocyanide of potassium, ten equivalents of which are changed by one equivalent of permanganic acid into five equivalents of ferricyanide of potassium. One equivalent of ferrocyanide of potassium (211.2) corresponds to one equivalent of Fe (28.)

## 2. *Solution of Ferrocyanide of Potassium.*

7.543 gm. of perfectly pure, dry, crystallized ferrocyanide of potassium, corresponding to 1 gm. of iron, are dissolved in water and the solution diluted to a liter. 10 cc. of this solution then correspond to exactly 0.010 gm. of iron. The solution is to be kept in a well-stopped bottle.

### *Titration of the Permanganate of Potassium Solution.*

100 cc. of the ferrocyanide of potassium solution (corresponding to 10 mgrm. of iron) are measured off with a pipette, diluted with about 50 cc. of water, acidulated with hydrochloric acid, the vessel placed on a piece of white paper, and the dilute solution of permanganate of potassium dropped into it with constant stirring until the occurrence of a reddish-yellow color in the fluid indicates that the conversion has been completed. Supposing we have used up to this point 20 cc. of permanganate of potassium solution, 1 cc. will, therefore, correspond to  $\frac{2.010}{20} = 0.1005$  mgrm. of iron. A second experiment must establish the accuracy. An oxalic acid solution which contains 1.125 gm. of crystallized oxalic acid in the liter, corresponding to 1 gm. of iron, may be used for the same purpose. In testing, 10 cc. of this solution, corresponding to 0.010 gm. of iron, are heated almost to boiling, a little dilute sulphuric acid is added, and it is titrated with the permanganate of potassium solution until it becomes red. The volume used up to this point corresponds to 0.010 gm. of iron. I prefer the latter method.

**C. Performance.** In order to ascertain the amount of iron in the urine by this method, it is necessary to evaporate it and ignite the organic matters. 100 cc. of urine, therefore, are evaporated to dryness in a platinum dish and the ash is obtained exactly according to § 60. After cooling, the saline mass is dissolved in hydrochloric acid, heated, water is added, and the solution is carefully transferred to a flask of 100 or 150 cc. capacity. Before the titration can be undertaken, the iron present as oxide must be reduced; a little sulphite of sodium is, therefore, added to the hydrochloric acid solution, and it is boiled until the fluid has become colorless and no more trace of sulphurous acid can be detected. When we have established the strength of the permanganate of potassium solution by means of the oxalic acid or ferrocyanide of potassium, the solution of iron is diluted to about 60 cc.; it



is allowed to become completely cool, the glass is placed on a piece of white paper, and the permanganate of potassium solution is dropped into it with constant stirring, until the fluid has assumed a faint rose-red color. Granted that 1 cc. of our solution of permanganate of potassium corresponded to 0.0005 grm. of iron, and that we have used 3 cc. up to the commencement of the end reaction, the 100 cc. of urine, therefore, contained  $3 \times 0.5$  mgrm. of iron = 0.0015 grm. The amount of iron found, multiplied by 1.43 gives the corresponding amount of ferric oxide; multiplied by 1.286 it gives the corresponding amount of ferrous oxide.

The method is a good one, and gives accurate results. It must be remembered that the red color produced by the last drop disappears after a time, and we must not allow it to lead us into error.

### § 73. ESTIMATION OF URIC ACID.

#### 1. *By Precipitating with Hydrochloric Acid.*

200 cc. of urine are put into a small beaker, 5 cc. of pure hydrochloric acid (sp. gr.=1.11) are added and the mixture thoroughly stirred with a glass rod; the beaker is then covered with a glass plate and allowed to stand at rest in a cool place with the temperature as low as possible for twenty-four or thirty-six hours. At the end of this time the uric acid will be found to have separated in crystals more or less colored, which are to be collected and washed on a weighed filter and subsequently dried.

But since paper is a very hygroscopic material, the weight of a dried filter cannot be determined directly. In this case, therefore, as in all others where bodies are to be collected on weighed filters and estimated, we make use of a simple contrivance and one which at the same time answers all requirements. Two watch glasses which are ground on the edge and therefore fit each other with perfect accuracy (fig. 36, *bb*) are selected; these are held together by a brass clamp *aa*, so that the filter *c* lying between them is hermetically sealed. In drying, the two watch glasses are placed one within the other, and with the filter lying on them are placed in the desiccator, fig. 15. When the latter has been heated for a long time to  $100^{\circ}$ ,



the watch glasses are placed together, the clamp is slid over them, and, after cooling over sulphuric acid, fig. 16, they are weighed.

FIG. 36.

The uric acid separated is collected on the filter thus dried, first by washing those crystals which are on the surface of the fluid on to it, when the rest of

the urine, which in most cases is clear, can be poured off, or, more safely, drawn off with a siphon, and then the uric acid which adheres to the walls and bottom of the glass is loosened with a feather with only a little of its beard left, or, better still, by a glass rod which has a small piece of rubber tubing drawn over its end, and transferred to the filter. For rinsing the glass and washing down the uric acid the filtrate first obtained, which is already saturated with uric acid, should be used, never water, since this would dissolve no inconsiderable amounts of the separated uric acid. When at last all of the uric acid is on the filter and the acid urinary fluid has run off even to the last drop, we begin to wash with *cold* water until the filtrate is no longer rendered cloudy by a solution of nitrate of silver. Large amounts of water must be avoided on account of the solubility of the uric acid. If only a small filter, having a radius of 1 to 1½ inch, is used, then 30 cc. of water are quite sufficient for the most complete washing in most cases. When this point is reached, the filter is taken from the funnel, laid on one of the watch glasses and dried for a long time in the air bath at 100°. The uric acid is then weighed exactly as before, fig. 36. What the apparatus has gained in weight is the uric acid which was contained in 200 cc. of urine.

This simple method has two sources of error. First, a certain amount of uric acid always remains in solution, and second, the uric acid separated always carries down a little coloring matter with it. However, if we accurately observe the above conditions and use a filter of 1 to 1½ inch radius which has first been thoroughly washed with hydrochloric acid and then with water before drying and weighing, the two sources of error mentioned above nearly counterbalance each other if only 30 cc. of water have been used in washing the uric acid. (Heintz.) This amount

of water will suffice in most cases, so that no further reaction can be obtained in the filtrate with nitrate of silver; but if for any reason a larger amount of wash water should be necessary, the two errors mentioned would no longer mutually cancel each other; that caused by the solubility of the uric acid would predominate, and, in order to counterbalance it, we must add 0.045 mgrm. to the amount of uric acid found by weighing for every cubic centimeter more than 30 of wash water which has been used. If, for example, the wash water amounts to 70 cc., we must add  $40 \times 0.045$  mgrm. to the amount of uric acid found by weighing.

If a urine in which we wish to estimate the uric acid contains albumen, we use the filtrate from the albumen coagulum which corresponds to a known volume of urine, and proceed with it as recommended above.

Numerous methods have been proposed for estimating the uric acid volumetrically, but all have proved unsuitable or wholly unserviceable. Permanganic acid certainly has a very energetic action on uric acid, but we cannot titrate it with permanganate of potassium directly in the urine, since many other substances are also destroyed by this energetic oxidizing substance. There is nothing left but to first precipitate the uric acid by an acid, filter, wash, dissolve in potassic hydrate, and titrate the solution with permanganate after acidulating. It would probably be simpler and more accurate under these circumstances, however, to weigh the washed and dried uric acid directly. The proposition to estimate the uric acid volumetrically by a solution of iodine in iodide of potassium has proved wholly impracticable.\*

Naunyn and Riess† lay stress on the fact that in the estimation of uric acid in diabetic urine the usual method of precipitating with hydrochloric acid, etc., does not suffice; they therefore precipitate the urine with acetate of mercury, decompose the precipitate with sulphuretted hydrogen, and determine the uric acid in the filtrate obtained.

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\* *Zeitschrift f. analyt. Chem.*, Band 7, p. 516.

† *Centralbl. f. d. med. Wissensch.*, 1870, p. 567. *Zeitschr. f. analyt. Chem.*, Band 9, p. 538.

## 2. *Estimation of Uric Acid by Salkowski's Method.*

Salkowski\* and Maly† have proved that all of the uric acid is not precipitated from the urine by hydrochloric acid, but that under certain circumstances considerable amounts remain in solution and can be precipitated from the filtrate as urate of magnesium and silver and can be determined quantitatively.

The method given by Salkowski for this purpose is the following: After the uric acid, precipitable by hydrochloric acid, has been filtered off and washed, the filtrate is neutralized with ammonia and precipitated with a strong magnesia mixture containing ammonia. Since by this, under certain circumstances and on long standing, urate of magnesium separates, it is filtered immediately, washed, and the filtrate and wash water treated with an ammoniacal solution of nitrate of silver in excess. The precipitate which results is filtered off preferably with the aid of the Bunsen pump, and washed until the wash water not only remains clear on acidifying, but also no longer gives any chlorine reaction on the addition of nitrate of silver. The precipitate is then washed into a flask, distributed by continued and energetic shaking, and decomposed by sulphuretted hydrogen, for which a somewhat long exposure is necessary. The fluid with the precipitate is then heated for a time, filtered, the filtrate evaporated to a small volume, strongly acidified with hydrochloric acid, and left at rest thirty-six or forty-eight hours. The uric acid thus obtained is collected on a small weighed filter, washed, dried, and weighed; it is pure with the exception of imponderable traces of sulphur.

Schwanert,‡ however, is of the opinion that the amount of uric acid which remains in solution after precipitation with hydrochloric acid may be readily determined by the ratio of solubility of uric acid in mixtures of hydrochloric acid and urine, as given by Voit and Zabelin§ and substantiated by Schwanert, so that the above-described somewhat detailed method is superfluous. According to Voit, Zabelin, and Schwanert, in every 100 cc. of the hydrochloric urinary fluid 0.0048 gm. of uric acid remain in solution, which must be added to that found directly.

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\* Zeitschrift f. analyt. Chem., Band 11, p. 234.

† Jahresbericht ü. d. Fortschritte d. Thierchemie, Band 2, p. 178.

‡ Annal. d. Chem. u. Pharm., Band 163, p. 153.

§ Annal. d. Chem. u. Pharm., Suppl. Band 2, p. 313.

In proof of his assertion Schwanert quotes fifteen comparative analyses in which the uric acid was determined according to Salkowski's method, and the amount obtained compared with that which remained dissolved in the fluid which was used, and reckoned at 0.0048 gm. for each 100 cc.

According to these fifteen double analyses the amount of uric acid which can be precipitated by hydrochloric acid and the solution of nitrate of silver is almost exactly the same as the amount precipitable by hydrochloric acid alone plus 0.0048 gm. for each 100 cc. of the filtrate, etc.

Salskowski \* acknowledges these objections of Schwanert to his method, and grants that he by no means regards the estimation of uric acid by precipitation with nitrate of silver as a commendable method, but that there continues to be an urgent need of a still better procedure for estimating the uric acid. But if Salkowski considers the agreement of the numbers obtained by Schwanert by the silver precipitation with those calculated by using the correction as simply accidental, we cannot agree with him, since, with a concurrence in fifteen cases, there can scarcely be any question of simple chance. As for myself, I used only the correction given by Schwanert for the uric acid remaining in solution after treatment with hydrochloric acid.

#### § 74. ESTIMATION OF KREATININ.

*A. Principle.* Kreatinin, as is known, gives with chloride of zinc a compound of kreatinin chloride of zinc ( $C_4H_7N_3O \cdot ZnCl$ ) quite readily soluble in hot water, and very insoluble in cold strong alcohol, which, according to my investigations, is eminently adapted for the gravimetric determination of this very important constituent of urine. 100 parts of kreatinin chloride of zinc correspond to 62.44 parts of kreatinin.

One part of kreatinin chloride of zinc requires 9217 parts of alcohol of 98 per cent., and 5743 parts of alcohol of 87 per cent. to dissolve it.

*B. Preparation of the Chloride of Zinc Solution.* Chemically pure oxide or carbonate of zinc is dissolved in pure hydrochloric acid, and the solution evaporated on the water bath to a

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\* Berichte d. d. chem. Gesellschaft, Band 5, p. 410.

very thick syrup, until all of the free hydrochloric acid is completely removed. The cooled residue is dissolved in quite strong alcohol and the solution diluted to 1.20 specific gravity.

*C. Performance.* 200 or 300 cc. of urine collected within twenty-four hours, mixed together and accurately measured, are treated with a little milk of lime until the reaction becomes alkaline, and a dilute solution of chloride of calcium is added as long as a precipitate results. After one or two hours it is filtered, filtrate and wash water are evaporated to a thick syrup on the water bath as quickly as possible, and, while still warm, are mixed with 40 or 50 cc. of alcohol of 95 per cent. The mass, thoroughly mixed, is put into a small beaker, the evaporating dish is rinsed with a small amount of alcohol, and it is left in a cool place six or eight hours for the complete separation of all that is precipitable. The fluid is then filtered through as small a filter as possible; at last, when all of it has passed through, the precipitate is collected on the filter and washed with a small amount of alcohol. If the whole filtrate amounts to much more than 60 cc. it is allowed to evaporate on a hot iron plate to 50 or 60 cc. When it has perfectly cooled,  $\frac{1}{2}$  cc. of the alcoholic solution of chloride of zinc is added, it is stirred for a long time, which aids the separation very much indeed, and it is then allowed to stand two or three days in a cool place, covered with a glass plate. When this time has expired, the crystalline precipitate is collected on a dry weighed filter between two watch glasses (fig. 36), making use always of the mother liquor for washing it on to the filter. When all of the kreatinin chloride of zinc has been collected on the filter and is completely freed from the mother liquor, it is washed with small quantities of alcohol until the latter passes through colorless and no longer reacts for chlorine. The washing should be thorough but not uselessly long. The filter, with the kreatinin chloride of zinc, is lastly dried at  $100^{\circ}$ , and weighed between the watch glasses. 100 parts of it correspond to 62.44 parts of kreatinin. The kreatinin chloride of zinc thus obtained is a faintly yellow-colored powder, which the microscope shows to consist of yellow transparent spheres of varying size, with sharp contours. According to my estimates this product contains about 94 per cent. of pure kreatinin chloride of zinc, but since the precipitation, on account of the solubility of this

body, is never absolutely complete, we can confidently regard it as pure, and for 100 parts of it reckon 62.44 parts of kreatinin; the two errors will then nearly counterbalance each other. But the alcoholic extract of the urinary residue must always be allowed to stand several hours, as specified, before it is filtered and the kreatinin precipitated, in order that everything precipitable, especially the chloride of sodium, shall have separated, since otherwise the kreatinin chloride of zinc is frequently mixed with cubes of chloride of sodium, which would render the entire estimation false. I therefore advise that the kreatinin chloride of zinc, after being weighed, should be moistened with absolute alcohol, and finally examined microscopically; it must show the forms described in § 3, C, 1, and be absolutely free from cubes of chloride of sodium.

This method gives satisfactory results. With pure kreatinin 99 and 99.2 per cent. instead of 100 were found. (Analytical Experiments.)

In diabetic urine the sugar must be destroyed before the kreatinin is determined. Of the daily amount of urine 500 or 1,000 cc. are treated with fresh pure yeast and allowed to stand in a moderately warm place until the fermentation is complete. It is then precipitated with milk of lime and chloride of calcium as described, filtered, evaporated, and the residue extracted with 100 cc. of alcohol of 95 per cent. After standing several hours the alcoholic solution is filtered off, evaporated to 50 cc., and after cooling precipitated with chloride of zinc solution as above. If the microscopic examination of the weighed kreatinin chloride of zinc should show admixture with foreign substances, a quantitative estimation of the zinc is made, and from this the kreatinin present is calculated. 100 parts by weight of kreatinin chloride of zinc correspond to 22.4 parts by weight of zinc oxide. (Winogradoff and Gaethgens.)\*

#### § 75. ESTIMATION OF ALBUMEN.

A. *Gravimetric.* The quantitative estimation of albumen depends, as the qualitative recognition of it does, on its coagulation by heat, and that this may be complete, a most careful observance of the precautions given already in § 23 is required.

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\* Zeitschrift f. analyt. Chem., Band 8, p. 100.

According to the greater or less quantity of albumen present 20, 50, or 100 cc. of the urine previously filtered are put into a correspondingly large beaker with a pipette, so that we do not get more than 0.2 or 0.3 of coagulated albumen, by which the whole estimation is very much facilitated. With concentrated urines, moreover, it is well to dilute the urine before heating. If, therefore, when there is a large amount of albumen only 20 cc. of urine are measured off, this is diluted with 80 cc. of water; 50 cc. of urine, with 50 cc. of water, etc. If, on the contrary, the amount of albumen is so small that 100 cc. of urine do not contain more than 0.2 or 0.3 gm. of albumen, a further dilution is not advisable. The beaker is then heated on the water bath for half an hour; if there is not enough free acid present, if a coarse flocculent coagulation does not occur, and if the supernatant fluid does not become completely clear, one or two drops of acetic acid are added with a glass rod and the heat is continued, whereupon a coarse flocculent coagulation of the albumen does ensue and the fluid becomes clear. An excess of acetic acid must be avoided, since a part of the albumen dissolves in the acid again if too much has been added, and would therefore escape calculation. But, on the other hand, the urine under no conditions should have an alkaline reaction, since a soluble alkaline albuminate, which does not coagulate at all on boiling, is formed.

We can treat the urine with acetic acid before heating, but in this case still more care is necessary, since, when too much acid has been added, coagulation does not take place on heating. If the urine is acid, the addition of acetic acid is not really necessary, although the coarse flocculent and complete coagulation of the albumen is at all events very much expedited thereby.

If the coagulation in thick flakes has been complete, the precautions mentioned having been observed, and if the supernatant fluid has become clear, filtration may be commenced.

The fluid which stands above the coagulum is first poured on a dried folded filter, which has been weighed and moistened with water, this fluid runs through clear and quickly if the amount of albumen is not too large and the urine has been sufficiently diluted, so that the coagulation has been complete, when last of all the greater part of the coagulum is placed on



the filter. When all of the fluid has passed through, the albumen is washed with hot water into the apex of the filter, which is easily accomplished. The beaker is now rinsed with hot water, the last particles of albumen are loosened with a feather and the whole is thus collected on the filter, which is then washed with hot water until the filtrate no longer gives any reaction with nitrate of silver and on being ignited leaves no residue on platinum foil. If the operation is performed in the manner I have described above, the filtration takes place very well and very rapidly, otherwise it is often very slow and tedious.

The filter is now carefully removed from the funnel, placed on one of the two watch glasses, fig. 36, and dried on the water bath at  $100^{\circ}$  until it no longer loses weight after cooling over sulphuric acid. Great care is to be exercised here, since the albumen, especially when we have too large an amount on the filter, usually cakes together into a horny mass, and, as it were, becomes covered with a dry crust, while moisture is still contained within it and can only be removed by very slow drying at  $100^{\circ}$  (six or eight hours). Therefore the drying operation can only be regarded as completed when two weighings agree, the filter having in the meantime been exposed to the given temperature for a considerable time. After deducting the weight of the watch glasses and of the filter from the weight last obtained, we obtain the quantity of albumen which was present, and which may then be calculated for the whole amount of urine.

The estimation of albumen performed in this manner is subject to two errors, for in the first place the albumen, in its coagulation carries down with it a little coloring matter, which cannot be removed even by prolonged washing with hot water. This is the reason why dried albumen in most cases appears to be yellow or even brown. However, this source of error is very inconsiderable and may be safely neglected. But frequently the earthy phosphates also separate with the albumen and naturally cause the amount of albumen to appear too great. In perfectly accurate estimations, therefore, the dried and weighed albumen, together with the filter, must be ignited in a weighed platinum crucible until all of the carbon has disappeared, which can be easily accomplished in a short time when the crucible lies obliquely. The increase in weight of the pla-



tinum crucible minus the known weight of the filter ash gives the amount of ash of the weighed albumen, which must be subtracted from the amount of albumen first found. In most cases this roundabout way is unnecessary; I have repeatedly satisfied myself that the amount of ash in albumen coagulated from a sufficiently dilute acid urine is very small and consequently has a very slight influence on the result.

20 cc. of a urine rich in albumen were diluted with 80 cc. of water, coagulated in a beaker on the water bath and the coagulum collected on a folded filter, thoroughly washed and dried at  $100^{\circ}$  to a constant weight. The albumen weighed 0.3573 gm., which calculated for the whole twenty-four hours' amount of urine (1,050 cc.) = 18.76 gm. After igniting and subtracting the filter ash there remained 0.0013 gm. of albumen ash. After subtracting this the twenty-four hours' amount of albumen was calculated at 18.69 gm. instead of 18.76 gm. first found.

B. *By Circumpolarization.* If the amount of albumen in a urine is not very small, the urine itself not too dark colored, and if it becomes perfectly clear on being filtered, the albumen may be estimated also by means of the polarizing apparatus of Soleil-Ventzke. The method is exactly the same as was described in the estimation of sugar in § 70, 3. If the color and transparency of the urine permit, an observing tube 200 mm. long should be used, and after being carefully filled and placed in the apparatus, by turning the compensator the two halves of the field of the double plate are made exactly isochromatic. The zero-point of the nonius now lies on the left side of the zero-point of the scale, and each division with a tube 200 mm. long corresponds to 1 gm. of albumen in 100 cc. of urine; and each division of the nonius to 0.1 gm. If, however, we have used a tube only 100 mm. long, the divisions of scale and nonius are to be multiplied by two in order to find the per cent. of albumen in 100 cc. of urine. If the urine does not become sufficiently clear by filtration alone, the turbidity may frequently be cleared up by a drop of acetic acid or a few drops of carbonate of sodium or milk of lime without thereby changing the specific rotation of albumen. After filtration the urine is clear enough in most cases to allow of its examination in the polarizing apparatus, in some cases, however, it fails. (Hoppe-Seyler.)

Since, as my abundant experience has shown, the cases are very rare in which the method of determining albumen quantitatively described under A cannot be performed, I content myself with merely mentioning here the other methods which have been proposed, for none of them equals in accuracy the gravimetric, which, properly performed, gives the desired result quickly and accurately.

1. *The Method of Bideker*\* depends on the fact that albumen in an acetic acid solution is completely precipitated by ferrocyanide of potassium. This procedure gives only approximate results, of which I have convinced myself several times. Also Thomas† states that if the albumen does not amount to 1·5 or 2 per cent., the results are wholly unreliable. In all cases in which the quantity of albumen was very small, Thomas found by Bödeker's method very much more albumen than by weighing.

2. *Vogel's Optical Method*.‡ The urine is rendered faintly acid with acetic acid, measured amounts of 4 or 6 cc., etc., are diluted to 100 cc. with water, heated to boiling, quickly cooled and tested by ascertaining whether the light from a stearine candle is still perceptible through a layer of the mixture 6·5 cm. thick. The experiment is repeated with different degrees of concentration until a dilution is reached at which the picture of the flame just disappears. The percentage of albumen in the urine is found by dividing the mean number 2·3553, obtained by Dragendorff by chemical analysis, by the number of cc. of urine used. Dragendorff performed thirty-five comparative analyses; three times differences of more than 0·1 were shown, eleven times of more than 0·05, so that of thirty-five analyses twenty-one corresponded with the gravimetric method to within 0·05. Masing obtained in seven comparative analyses differences up to 20 per cent., which were plus as well as minus.

3. *Lang, Haebler, and Bornhardt*§ calculate the amount of albumen in the urine from the difference in the specific gravity of the urine before and after it has been coagulated by heating. According to Haebler this difference must be multiplied by 210,

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\* Annal. d. Chem. u. Pharm., Band 111, p. 195.

† Schmidt's Jahrbücher, Band 120, p. 171.

‡ Zeitschrift f. analyt. Chemie, Band 7, p. 152. Masing, Beiträge zur Albuminometrie, Dorpat, 1867.

§ Zeitschrift f. analyt. Chem., Band 7, p. 513, und Band 9, p. 149.

according to Bornhardt by 415, in order to find the percentage of albumen in the urine. My experiments show that Haebler's quotient is absolutely false, and also that Bornhardt's number yields with very careful manipulation only tolerable results when the amount of albumen in the urine is not too small, but with the low specific gravity of albumen and its small amount in the urine the limits of error are very great. Stscherlakoff and Chomjakoff\* arrived at the same results.

4. *Méhu's Method.*† To 100 cc. of urine, which must not contain more than 0.2 to 0.4 albumen, 2 cc. of nitric acid are added, and then 10 cc. of a mixture of equal parts of crystallized carbolic and glacial acetic acids with two parts of alcohol of 90 per cent. It is filtered, first washed with water, to which  $\frac{1}{2}$  per cent. of carbolic acid has been added, and later with water containing alcohol, dried at 110° C., and weighed. The carbolic acid precipitates the albumen without forming a chemical compound with it.

According to examinations by Schacht,‡ Méhu's method, especially in urines which contain a small amount of albumen, has no sort of advantage over the one described by me.

5. *Method of P. Liborius.*§ 50 or 100 cc. of urine are treated in a beaker with four or five times its volume of alcohol of 85 per cent. After twenty-four hours the coarse flocculent precipitate is collected on a filter, washed, dried at 110° or 115° C. and weighed. The precipitate is then ignited in a weighed platinum crucible, the ash which remains, and is not inconsiderable in quantity, is weighed, and its weight deducted from that first obtained. By this procedure Liborius always obtained more albumen than by coagulation or by the old method of Berzelius, which, moreover, yielded results agreeing with those obtained by coagulation. The reason of this is quite apparent, since alcohol not only precipitates albumen from the urine, but all albuminous bodies also, especially peptone, which, according to Senator,|| is never absent from any albuminous urine, as

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\* Zeitschrift f. analyt. Chem., Band 9, p. 537.

† Journ. d. Pharm. et de Chim., 1869, p. 95. Zeitschr. f. analyt. Chem., Band 8, p. 523.

‡ Archiv d. Pharm., Band 139, p. 19.

§ Deutsch. Archiv f. klin. Med., Band 10, p. 319.

| Virchow's Archiv, Band 60, p. 488.

well as the albuminous bodies mentioned by C. Gerhardt,\* which are not identical with albumen, and lastly, uric acid, mucus, and some other substances. Therefore, we cannot let the precipitation with alcohol pass as a method of estimating albumen.

6. *L. Girgensohn's Method.*† This method is founded on the fact that tannin completely precipitates albumen, and that all of the tannin can be withdrawn again from the compound of tannin and albumen by boiling with alcohol. In performing the test a definite quantity of urine is treated with half its volume of a 20 per cent. solution of chloride of sodium, and then as much solution of tannin is added as is necessary for the complete precipitation of the albumen. The precipitate is collected in a weighed filter, washed with distilled water until the chlorine reaction disappears, and then with boiling alcohol as long as any tannin can be detected in the filtrate. The residue is dried and weighed. It might be well to remove the uric acid first by rendering it slightly acid with acetic acid, and allowing it to stand in the cold.

This method, also, is not free from the criticism which must be made of the precipitation with alcohol. Tannin by no means precipitates the albumen alone from the urine, but at the same time a number of other bodies.

## § 76. CALCIUM AND MAGNESIUM.

### I. ESTIMATION OF CALCIUM.

A. *Principle.* The method of estimating calcium depends on the fact that all of the calcium is precipitated from an acetic acid solution of the phosphate of calcium in the form of an oxalate by oxalate of ammonium, and that oxalate of calcium is transformed by a red heat into carbonate of calcium and caustic lime, whose amount is determined by standard solutions of hydrochloric acid and sodic hydrate.

B. *Preparation of the Solutions.*

1. *Standard Hydrochloric Acid.*

The hydrochloric acid which is used for this estimation of

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\* Centralblt. f. d. med. Wissenschaft., 1869, p. 174.

† Deutsch. Archiv f. klin. Med., Band 11, Heft 6.

calcium is best so standardized that each cc. corresponds to exactly 10 mgrm. of calcic oxide. One liter of the acid, therefore, must saturate 10 gm. of calcic oxide, or 18.93 gm. of carbonate of sodium. To prepare such an acid we twice weigh off an accurate quantity (about 1 or 1.2 gm.) of pure carbonate of sodium, previously ignited, and dissolve each portion separately in a flask in water, heat to boiling, after the solution is treated with a few drops of tincture of litmus, and then let the dilute hydrochloric acid flow into it until the blue color of the solution has changed to onion red, which does not disappear again on further boiling. (The purpose of the boiling is to remove the carbonic acid which has been set free, so that the transition of the wine-red color, which is caused by the carbonic acid, into the onion red shall come out sharply.) The experiment is repeated with the second quantity of carbonate of sodium, and from the results obtained the quantity of hydrochloric acid in the liter is reckoned by taking the average of the two. If, for example, we have found that one liter of the hydrochloric acid corresponds to 41.4 gm. of carbonate of sodium, then 457 cc. will exactly saturate 18.93 gm. If we, therefore, measure off 457 cc. from the hydrochloric acid thus tested, and dilute it to a liter, it has the required strength. 1 cc. then corresponds to 0.0189 gm. of carbonate of sodium, or 0.010 gm. of CaO. A control experiment with carbonate of sodium must confirm the accuracy of the dilution.

## 2. *Standard Sodid Hydrate.*

The sodic hydrate must exactly correspond to the hydrochloric acid, 10 cc. of it must, therefore, exactly saturate 10 cc. of the hydrochloric acid, so that after the addition of the last drop of the 10 cc. of sodic hydrate, the red color of the hydrochloric acid changes to a clear blue. We must be especially careful that the sodic hydrate is completely free from carbonic acid, so that the transition of color may be sharply recognized. 10 cc. of the hydrochloric acid are now measured off with a pipette, it is allowed to flow into a small beaker, it is colored red with a few drops of tincture of litmus, and then the sodic hydrate is added until it is a clear blue. If 8 cc. of sodic hydrate have been required to 10 cc. of hydrochloric acid, we measure off 800 cc. and dilute it to a liter. Equal volumes of the two will then accurately saturate each other. The accu-

racy of the dilution is tested by a new experiment; if after the last drop of the 10 cc. of sodic hydrate the red color of the 10 cc. of hydrochloric acid has become a clear blue, the sodic hydrate is fit for use in the estimation.

*C. Performance.* Exactly 100 or 200 cc. of the urine previously filtered are measured off with a pipette, allowed to flow into a beaker, and ammonia is added until an abundant precipitate has taken place, which is then caused to disappear by the careful addition of acetic acid. The calcium is precipitated from the acetic acid solution thus obtained, which must contain only a few drops of acetic acid in excess, by oxalate of ammonium, and the glass is allowed to stand covered in a warm place until the precipitate has completely settled and the supernatant fluid has become perfectly clear. In most cases after six or eight hours the fluid can be drawn off clear by a siphon, which is always to be preferred to slow filtering when it can be performed without loss. The rest of the fluid with the calcic oxalate is poured on to a small filter free from calcium and thoroughly washed with water. (Filtrate and wash water are put aside for determining the magnesium.) The filter and the precipitate, still moist, are placed in a small platinum crucible, dried and ignited until all of the carbon is consumed. The lime, which has become partly caustic, is carefully rinsed into a small flask, 10 cc. of the standard hydrochloric acid are added and cautiously warmed until the whole is dissolved and the carbonic acid is expelled. Then after the solution has been colored faintly red by two or three drops of tincture of litmus, the non-saturated part of the hydrochloric acid is titrated back with the sodic hydrate solution until the blue color appears. If the number of cc. of sodic hydrate used up to this point are subtracted from the 10 cc. of hydrochloric acid added, we obtain the number of cc. saturated by the lime, each one of which corresponds to 10 mgrm. of calcic oxide. If then we multiply the number of cc. of hydrochloric acid saturated by 10, we obtain directly the percentage of lime in the urine, if 100 cc. were taken for the estimation. (See Analytical Experiments.) If we wish to calculate the lime found as phosphate, 1 cc. of the hydrochloric acid corresponds to 18.45 mgrm. of  $3\text{CaOPO}_4$ .

*Gravimetric Estimation.* We proceed as above by precipi-

tating the calcium in the form of oxalate from 200 cc. of urine made acid with acetic acid. The washed and dried calcic oxalate, freed from the filter, is then placed in a weighed platinum crucible and ignited for a considerable time after the filter has been completely reduced to ashes on the cover. After cooling the crucible, the calcium, which has become partially caustic during the ignition, is moistened with a few drops of pure dilute sulphuric acid, when a loss may easily occur, and, therefore, the crucible must be covered as closely as possible during the operation. After heating a second time the calcium remains behind as a sulphate; the crucible is allowed to cool over sulphuric acid and is weighed. After subtracting the weight of the crucible and filter ash we obtain the amount of sulphate of calcium from which the corresponding amount of phosphate of calcium is reckoned. More easy still than evaporating and heating to a red heat with sulphuric acid is the conversion of the calcic oxalate into sulphate by pure ammonium sulphate. (Schrötter.)

Three equivalents of sulphate of calcium correspond to one equivalent of phosphate of calcium, having the composition  $3\text{CaO}, \text{PO}_5$ . If, therefore, we multiply the amount of sulphate of calcium obtained by  $\frac{1}{3} \frac{5}{4} = 0.7598$ , we obtain the corresponding amount of phosphate of calcium. If, on the other hand, we wish to reckon the sulphate of calcium as  $\text{CaO}$ , we must multiply the amount found by 0.4118.

## II. ESTIMATION OF THE MAGNESIUM.

1. *By Weighing.* The fluid filtered from the calcic oxalate is treated with ammonia until the reaction is alkaline, by which all of the magnesium is precipitated as ammonio-magnesian phosphate. When the precipitate has completely settled after a few hours, it is collected on a filter, the weight of whose ash is known, washed thoroughly with water, to which  $\frac{1}{4}$  of its volume of ammonia has been added, and dried. When this is accomplished, the precipitate is separated as completely as possible from the filter, it is put into a weighed platinum crucible, the filter is folded, and a thin platinum wire wound round it spirally, and it is ignited in the upper cone of the flame, which abounds in oxygen. This operation with phosphate of magnesium, otherwise so wearisome, is rendered very much



easier and shorter by this procedure; the ash becomes pure and white after a very short time. When the ignition has been accomplished the filter ash is added to the precipitate, the cover is placed on the crucible and it is heated a long time, at first very gently, but at last at the strongest red heat, with the cover off; it is then allowed to cool over sulphuric acid and weighed. The ammonio-magnesian phosphate precipitated from the urine in this way is, however, always mixed with organic matters, especially uric acid, which on heating yield a carbon difficult to ignite, and which, therefore, renders a very long-continued ignition of the precipitate necessary and with the crucible uncovered. It is, therefore, best to place a small piece of nitrate of ammonium on the ammonio-magnesian phosphate in the crucible after the filter has been ignited in the manner described, moisten it with a drop of water, dry, and heat first very gently, and lastly to a powerful red heat. The charcoal completely disappears, and we obtain the phosphate of magnesium very readily in this manner of dazzling whiteness. The ammonio-magnesian phosphate becomes pyrophosphate of magnesium ( $2\text{MgO}, \text{PO}_3$ ) on ignition; after subtracting the weight of the crucible and the filter ash an amount remains behind which, added to the quantity of pyrophosphate of calcium calculated and found, gives the whole amount of earthy phosphates (phosphates of calcium and magnesium) in the urine taken. If, however, we wish to calculate the pure phosphate of magnesium found ( $2\text{MgO}, \text{PO}_3$ ) as pure oxide ( $\text{MgO}$ ), we must multiply the amount obtained by  $\frac{40}{111}$ , that is  $= 0.3604$ , since 111 parts of pyrophosphate of magnesium correspond to 40 of pure magnesian oxide.

The earthy phosphates are determined more accurately and quickly in two amounts of urine, as follows:

a. The amount of phosphate of calcium ( $3\text{CaO}, \text{PO}_3$ ) in 200 cc. of filtered urine is accurately determined according to the method given in § 76, I. C. Each cc. of hydrochloric acid saturated corresponds to 18.45 mgrm. of phosphate of calcium.

b. Another 200 cc. of the filtered urine are precipitated with ammonia and allowed to stand six or twelve hours to completely separate and deposit all of the earthy phosphates. The fluid is then drawn off with a siphon, as far as this can be done without loss; the precipitate is collected on a filter, the



weight of whose ash is known, it is washed with water containing ammonia (three parts of water and one part of ammonia), and the magnesium estimated exactly as was indicated in § 76, II. 1. This second estimation gives the whole amount of earthy phosphates ( $2\text{MgO}, \text{PO}_4 + 3\text{CaO}, \text{PO}_4$ ) contained in the urine. If we subtract the phosphate of calcium found in 1 from it, the remainder is the amount of phosphate of magnesium in the urine.

2. *Volumetrically.* The magnesium is precipitated from 200 cc. of urine by ammonia, after the calcium has been removed by oxalate of ammonium; the ammonio-magnesian phosphate is collected on a small filter after a few hours and washed with water containing ammonia. The filter is then broken through with a glass rod, the precipitate washed into a beaker and dissolved with acetic acid. (If a little uric acid remains behind here, as has repeatedly happened in my analyses, the solution is best filtered from it.) The phosphoric acid is then determined in the fluid obtained exactly according to § 67, C, b. The amount of phosphoric acid found multiplied by 0.563 gives the corresponding amount of pure magnesia ( $\text{MgO}$ ); on the other hand, multiplied by 1.563 it gives the corresponding quantity of pyrophosphate of magnesium.

### III. INDIRECT ESTIMATION OF CALCIC AND MAGNESIC PHOSPHATES.

As is known there is no true separation attained by indirect analyses, but ulterior circumstances are brought about, from which we can calculate the acids and bases found together. If, for example, we have to determine potassium and sodium, the analysis can be made in such a manner that the two are changed into sulphates; if these are weighed and the whole amount of sulphuric acid in them determined, the amounts of potassium and sodium can be calculated from these data. This is the case with the calcium and magnesium contained in the urine in combination with phosphoric acid. To perform this estimation we precipitate the earthy phosphates in two specimens of 200 cc. of filtered urine by means of ammonia, filter it after a few hours, and determine one amount gravimetrically according to § 76, II. 1. The second amount is washed into a beaker, dissolved in acetic acid, and the phosphoric acid in it titrated

exactly according to § 67, C, b. The result is calculated for the twenty-four hours' amount of urine.

We now know :

a. The amount of the earthy phosphates

$$\left. \begin{array}{l} (\text{CaO})_2, \text{PO}_5 \\ (\text{MgO})_2, \text{PO}_5 \end{array} \right\} \text{ in twenty-four hours.}$$

b. The amount of phosphoric acid for twenty-four hours corresponding to the calcium and magnesium.

An example will now explain the calculation in the simplest and clearest manner.

Let us assume that the above estimations had shown that a daily amount of urine contained 1 gram. of earthy phosphates, and the phosphoric acid combined with the earths amounted to 0.579 gram. The amounts of calcic and magnesian phosphates are reckoned as follows :

If all the  $\text{PO}_5$  were combined with calcium, the earthy phosphates should weigh 1.264 gram., according to the following proportion :

$$\begin{array}{ccccccc} 71 & : & 155 & = & 0.579 & : & x. \\ (\text{PO}_5) & & [(\text{CaO})_2, \text{PO}_5] & & \text{(amount of } \text{PO}_5 \text{ found.)} & & \\ & & x=1.264 \text{ gram.} & & & & \end{array}$$

Since the total earthy phosphates, however, weigh less (gram. 1), phosphate of magnesium is also present in an amount proportional to the difference.

$$1.264 - 1.000 = 0.264.$$

This quantity of magnesian-phosphate is obtained from the following proportion :

The difference between the equivalents of phosphate of calcium (155) and phosphate of magnesium (111), that is 44, is to the equivalent of phosphate of magnesium (111), as the difference found, 0.264, is to the phosphate of magnesium present.

$$\begin{array}{l} 44 : 111 = 0.264 : x. \\ x = 0.666 \text{ gram. } (\text{MgO})_2, \text{PO}_5. \end{array}$$

We have then the total earthy phosphates  $\epsilon$   $= 1.000$  gram.

The calculated amount of phosphate of magnesium  $= 0.666$  “

$$\text{Leaving } (\text{CaO})_2, \text{PO}_5 \quad = \overline{0.334} \text{ gram.}$$

From this consideration the following short, universally applicable method of calculation may be deduced :

The amount of phosphoric acid in the mixture is multiplied by 2.1831, from the product the amount of the earthy phosphates is subtracted, the remainder is multiplied by 2.5227, and the product is the amount of the phosphate of magnesium contained in the mixture. If we designate the amount of the earthy phosphates found by S, and the  $\text{PO}_5$  obtained by P, the calculation may be simply expressed by the following formula :

$$(P \cdot 2.1831 - S) 2.5227.$$

If we wish to calculate the calcium and magnesium in the amounts of phosphate of calcium and of magnesium obtained, the following formulæ are used :

$$\begin{aligned} (\text{CaO})_3\text{PO}_5 &\times 0.5420 = \text{CaO}. \\ (\text{MgO})_3\text{PO}_5 &\times 0.3604 = \text{MgO}. \end{aligned}$$

## § 77. ESTIMATION OF AMMONIA.

*A. Principle.* This method of estimating the quantity of ammonia, first mentioned by Schlösing, depends simply on the fact that an aqueous solution containing free ammonia suffers its ammonia to escape at ordinary temperatures in a relatively short time when exposed to the air, and that dilute sulphuric acid absorbs all of the ammonia contained in a closed space. If, therefore, we place an aqueous solution of ammonia together with a measured volume of standard sulphuric acid in a closed space, all of the ammonia in a short time will have combined with the sulphuric acid and have saturated an equivalent amount of it, which may be readily ascertained by titrating back the non-saturated portion with a standard sodic hydrate solution.

### *B. Preparation of the Solutions.*

#### *1. Standard Sulphuric Acid.*

14 grm. of hydrated sulphuric acid are diluted with 200 grm. of water, and when the mixture has become cool the strength of this dilute acid is determined in the usual way by precipitating two specimens, of 10 cc. each with chloride of barium. If the two analyses agree we accept the result as correct. If, for example, we find that 10 cc. of the dilute acid contain 0.505 grm. of sulphuric acid, then they will be exactly saturated by

0.2146 grm. of ammonia ( $\text{NH}_3$ ); therefore, 1 cc. of the dilute acid corresponds to 0.02146 grm. of ammonia ( $\text{NH}_3$ ).

2. *Standard Sodid Hydrate Solution.*

We determine how large a volume of a good sodid hydrate solution, free from carbonic acid, is required to saturate 10 cc. of the standard sulphuric acid. For this purpose 10 cc. of the standard sulphuric acid are put in a small beaker, a few drops of tincture of litmus are added, and the sodid hydrate solution dropped from a pipette until the fluid just becomes blue. If we have used 30 cc. of the sodid hydrate solution up to this point, we know that each cc. of it corresponds to 0.00715 grm. of ammonia, because 10 cc. of the sulphuric acid (corresponding to 0.2146 grm. of  $\text{NH}_3$ ) have been exactly saturated by 30 cc. of the sodid hydrate solution.

C. *Process.* A flat glass or porcelain vessel (a beaker broken off an inch from the bottom is suitable for the purpose) is placed on a plate of ground glass which is smeared with tallow, and 10, or better, 20 cc. of the urine which is to be tested, freed from mucus by filtration, are introduced into it. A triangle made of glass rod is then laid on the vessel, and on the triangle a flat dish with low sides containing 10 cc. of the standard sulphuric acid is placed. A bell glass with a ground edge and smeared with tallow is then placed over the whole apparatus, so that an hermetically closed space is thus obtained.

Fig. 37 shows the whole apparatus. When the apparatus is all prepared, the bell glass is raised, a sufficient quantity of milk of lime (10 cc.) is added to the urine from a pipette not drawn out at the end, and the bell glass is immediately firmly replaced. After forty-eight hours the whole of the ammonia has been expelled from the 10 or 20 cc. of urine and absorbed by the sulphuric acid. If the

FIG. 37.

non-saturated sulphuric acid is titrated back with the sodid hydrate solution, we ascertain the amount saturated by the am-

monia, and consequently the quantity of ammonia in the 20 cc. of urine.

Example :

10 cc. of sulphuric acid = 0.505 grm.  $\text{SO}_2$  = 0.2146 grm.  $\text{NH}_3$ . They require 30 cc. of sodic hydrate solution ; 1 cc. of sodic hydrate solution, therefore, corresponds to  $\frac{0.2146}{30} = 0.00715$  grm. of  $\text{NH}_3$ .

At the end of the experiment 26 cc. of the sodic hydrate solution have been required in titrating back. Therefore, an amount of  $\text{NH}_3$  has been evolved which corresponds to 4 cc. of the sodic hydrate solution. The 20 cc. of urine, therefore, contain  $4 \times 0.00715 = 0.0286$  grm.  $\text{NH}_3$  = 1.43  $\text{NH}_3$  per thousand. From my own experiments it appears that perfectly normal fresh urine does not undergo the alkaline fermentation in forty-eight hours ; but these experiments must not be taken as the rule in all cases, since many urines, as we well know, very soon become alkaline. I consider it safer, therefore, to make a control experiment, in addition to the regular estimation of ammonia, by placing a like amount of the same urine in a second apparatus without milk of lime and observing the result. If we find that the urine readily becomes decomposed, it is better to first remove the coloring and extractive matters. We prepare for this purpose a mixture of acetate and basic acetate of lead solutions, an equal volume of each, measure off 30 cc. of the urine, add to it an equal quantity of the lead solution, filter, and take 40 cc. from the clear filtrate corresponding to 20 cc. of urine for the estimation of the ammonia. This precaution is quite unnecessary with a normal fresh urine, as my experiments show.\* This method gives very satisfactory results. (Analytical Experiments.)

#### § 78. ESTIMATION OF THE AMMONIA AND POTASH BY MEANS OF PLATINIC CHLORIDE.

A measured quantity of urine, 20 or 30 cc., are placed in a beaker, and a sufficient quantity of platinic chloride and three times its volume of a mixture of alcohol and ether are added. After twenty-four or thirty-six hours, when no further precipi-

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\* Journ. f. pract. Chemie, Band 64, p. 177.

tation is seen to take place, it is filtered, well washed with alcohol to which a little ether has been added, and dried. The precipitate, together with the filter, is then placed in a platinum crucible and ignited, the crucible being covered at first, until the carbon of the filter is wholly consumed, which process may be very much hastened by giving the crucible an oblique position. The remaining mass is then treated with hot dilute hydrochloric acid as long as the acid takes up anything; the platinum which remains behind is placed on a filter, the weight of whose ash is known, carefully washed with hot water, and the filtrate obtained preserved for estimating the potassium by the method to be mentioned directly. After igniting and weighing, by subtracting the weight of the filter ash and crucible, we obtain the quantity of platinum which corresponds to the amount of ammonia and potassium contained together in the urine.

In order now to determine the quantity of the potassium, the hydrochloric acid solution, together with the wash water which contains the whole of the potassium, is reduced to a small volume (1 or 2 cc.) by evaporation, it is precipitated by thirty drops of platinic chloride solution and a mixture of alcohol and ether as mentioned above. After twenty-four hours the precipitate which is obtained, and which contains all of the potassium as potassio-platinic chloride, is placed on a filter, washed with alcohol and ether, dried, ignited with the filter as above, extracted with hydrochloric acid, the remaining platinum collected on a filter, the weight of whose ash is known, dried, ignited, and weighed. After subtracting the weight of the filter ash, we obtain the quantity of platinum which corresponds to the potassium. The difference between this amount of platinum and that obtained at first corresponds to the quantity of ammonium. If, for example, we find the whole amount of platinum to be 0.1980 gm. for the potassium and ammonium contained in 30 cc. of urine, and for the potassium alone by the second estimation 0.1330, there remains for ammonia 0.065 gm. of platinum (0.1980 - 0.1330).

One hundred parts of platinum correspond to 17.182 parts of ammonia, therefore 0.065 platinum ( $100:17.182 = 0.065:x$ )  $x = 0.01116$  ammonia in 30 cc. of urine.

We calculate in the same way the amount of potassium pres-

ent from the amount of platinum employed in separating it; 100 parts of platinum correspond to 47.61 parts of potassic oxide.

### § 79. ESTIMATION OF THE POTASSIUM AND SODIUM.

A. *Direct Determination.* 30 cc. of urine are mixed with 30 cc. of baryta solution (two volumes of baryta water and one volume of a cold saturated solution of nitrate of barium, see § 65, B, 3), it is allowed to stand for a time, filtered, 40 cc. of the filtrate are measured off, corresponding to 20 cc. of urine, and evaporated to dryness in a platinum capsule on the water bath. The residue is then heated over a free flame, at first very gently to avoid decrepitation and too sudden combustion, afterward strongly, and the heat is continued until the greater part of the carbon has been consumed. Yet we must guard against too strong a heat lest a part of the chlorides should volatilize. The residual mass is then extracted with hot water, acidulated with hydrochloric acid, and treated, without previous filtration, with a solution of ammonia and carbonate of ammonium as long as a precipitate is thrown down, it is filtered, the precipitate thoroughly washed, and the filtrate, after acidulating with hydrochloric acid, is evaporated again to dryness in the platinum capsule. After the residue has become perfectly dry it is carefully heated to drive off the ammonium salts, but in such a manner as not to suffer any loss from decrepitation, the residue is again dissolved in a little water, a few drops of ammonia and carbonate of ammonium are again added, the mixture filtered, the precipitate carefully washed and the filtrate again evaporated to dryness, but this time in a previously weighed platinum capsule. The thoroughly dry residue is gently heated to drive off the ammonium salts, it is then left to cool in the desiccator and weighed. We thus obtain the whole quantity of potassium and sodium in the form of chlorides. To separate the two the weighed amount of alkaline chlorides is dissolved in a little water, chloride of platinum added in considerable excess, and the mixture evaporated almost to dryness on the water bath. The residue is then treated with alcohol of 80 per cent. and allowed to stand several hours with frequent stirring. When the sodio-platinic chloride is dissolved, and the supernatant fluid has a deep yellow color, a sign that sufficient chloride of platinum has been added, the potassio-platinic chloride is

collected on a filter which has previously been dried at 100° C. and weighed, washed with alcohol, dried at 100° C. and weighed.

From the potassic-platinic chloride obtained the corresponding amount of chloride of potassium is calculated (100 parts of potassio-platinic chloride correspond to 30.51 parts of chloride of potassium), and this subtracted from the whole quantity of the alkaline chlorides gives as the difference the amount of chloride of sodium.

The amount of chloride of potassium obtained gives when multiplied by 0.6317 the corresponding amount of potassic oxide; the chloride of sodium multiplied by 0.5302 gives the corresponding amount of sodic oxide.

*B. Indirect Determination.* The potassium and sodium can be calculated indirectly, though this method is inferior to the former in accuracy. The principle of the indirect analysis has already been given in § 76, III. After the whole quantity of chloride of potassium and chloride of sodium has been accurately determined by weighing, according to A, the saline mass is dissolved in water, the solution is introduced into a beaker, the vessel thoroughly washed with water, and, after the addition of a few drops of a solution of neutral chromate of potassium, the whole amount of the chlorine is determined by means of a standard solution of nitrate of silver according to § 66. If we know the total amount of the chlorides of potassium and sodium, as well as the total amount of chlorine, the quantity of potassium and sodium can be reckoned from these data.

The amount of chlorine in the mixture is multiplied by 2.1029, the amount of the metallic chlorides is subtracted from the product, and the remainder is multiplied by 3.6288. We thus find the quantity of chloride of sodium contained in the saline mass, and this, subtracted from the total metallic chlorides, gives the quantity of chloride of potassium.

Chloride of potassium  $\times 0.6317$  = potash (KO). Chloride of sodium  $\times 0.5302$  = soda (NaO).

Experiments to determine the quantity of potassium by precipitating the previously concentrated urine with tartaric acid did not give favorable results. On account of the impurity of the acid tartrate of potassium obtained the results were constantly too high. (Salkowski.)\*

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\* Pflüger's Archiv, Band 6, p. 209.



## § 80. ESTIMATION OF THE CARBONIC ACID.

According to Marchand,\* the free carbonic acid in the urine can be estimated in the following way: About 100 cc. of the urine to be tested are placed in a glass flask which is fitted with an air-tight, doubly perforated stopper. A tube which dips into the urine and is drawn out to a fine, easily fusible point at the other end, is passed through one opening of the stopper; while through the second opening a doubly bent tube is passed, one of whose arms enters an empty flask through an air-tight stopper. This flask is connected by a second tube with a similarly arranged flask filled with clear baryta water, which again is connected with one or two flasks half-filled with baryta water. The last of these is connected with an air pump. When the apparatus is prepared, the urine is heated on the water bath to 50° or 60° C. and the air slowly exhausted. The fluid soon commences to boil and to distil over into the empty flask, and the baryta solutions become cloudy from the separation of carbonate of barium. After half or three-quarters of an hour the fine point of the first tube is broken off and air is drawn through the apparatus. The precipitated carbonate of barium is carefully filtered off, and, after washing, dissolved in hydrochloric acid, precipitated again by sulphuric acid, and weighed as sulphate of barium. From the quantity thus obtained we calculate the carbonic acid which was present. 116.5 parts by weight of sulphate of barium correspond to 22 parts by weight of carbonic acid.

## § 81. ESTIMATION OF THE TOTAL NITROGEN IN THE URINE.

As is well known the urine contains nitrogen in very different forms, such as urea, uric acid, kreatinin, ammoniacal salts, etc. It may be of importance in answering physiological questions to determine quantitatively the entire amount of nitrogen eliminated with the urine in these different forms; therefore I give here the method given by Voit and Seegen for this purpose.

Since in estimating urea in the urine by Liebig's method, not only the urea is precipitated, but other nitrogenous constitu-

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\* Journ. für pract. Chemie, Band 44, p. 253

ents of the urine also, such as kreatinin, etc., form compounds with the mercuric nitrate, we can, according to the investigations of Voit,\* Parkes, and Wollowicz,† calculate from the urea found by Liebig's method, the total quantity of nitrogen with tolerable accuracy. Voit found in an average of seventeen combustion analyses in 700 cc. of human urine 9.31 grm. of nitrogen, while 9.4 grm. were reckoned from the urea found. Parkes and Wollowicz found in twenty-six combustion analyses that the amount of nitrogen eliminated in twenty-four hours averaged 16.46 grm., while from the urea found by Liebig's method after precipitating the chlorine, 16.34 grm. of nitrogen were obtained on the average. S. Schenk‡ obtained results which differed somewhat; he determined the nitrogen in human urine by combustion with soda-lime and by Dumas's method, and in addition calculated from the urea obtained. While the two methods of estimating the nitrogen gave nearly the same results, the calculations from the urea showed deviations. In an average of eight estimations, combustion gave 0.1395 grm. of nitrogen for 10 cc. of urine, while 0.1385 grm. was reckoned from the urea. The greatest deviations which Liebig's method gave in comparison with the direct determination of nitrogen amounted to  $-0.014$  and  $+0.021$  for 10 cc. of urine; if the twenty-four hours' quantity of urine had amounted to 1,000 cc., there would have been found 1.4 grm. of nitrogen too little or 2.1 grm. too much. Schenk on the strength of his experiments declares Liebig's method unserviceable, as well for estimations of urea as of nitrogen, and, consequently, for all experiments upon the metamorphosis of tissue; and since the estimation of urea by the method of Heintz always gave less nitrogen than by other methods, he regards it as the most suitable for ascertaining the true quantity of urea in the urine. Moreover, it has been shown that the deviations of the direct estimations of nitrogen and the quantities calculated from the urea by Liebig's method nearly balance in long series of experiments, and such only come in question in experiments upon the metamorphosis of tissue, by the averages reported by Voit,

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\* Zeitschrift f. Biologie, Band 2, p. 469.

† Chem. Centralblatt, 1870, p. 681.

‡ Centralblatt f. d. med. Wissenschaften, 1869, p. 858. Wiener Sitzungsbericht. 59, p. 162.

Parkes, and Wollowicz, as well as by those obtained by Schenk also. In conclusion, with regard to the estimation of urea by the method of Heintz and Ragsky, concerning which Schenk asserts that there is no suspicion that the results could prove too small, and that we know of no other body in the urine than urea which on heating with sulphuric acid yields ammonia, Heintz\* himself has shown that his method yielded for 1,000 parts of urine about 0.3 urea too much, since kreatin, oxaluric acid, and the extractive matters also gave a little ammonia on heating with sulphuric acid. Liebig's method will not deviate much more from the truth, and, therefore, will probably only be abandoned when a method is found which with the same ease will yield really absolute figures for the urea.

*A. Principle.* All organic nitrogenous bodies which do not contain the nitrogen in the form of nitric acid, etc., are so decomposed by ignition with soda-lime that all of the nitrogen escapes in the form of ammonia, which can be easily collected in sulphuric acid of known strength, and be determined by titration. One equivalent of  $\text{NH}_3=17$ , corresponding to one equivalent of  $\text{N}=14$ .

*B. Preparation of the Solutions.* It is well to use for this purpose a dilute sulphuric acid, which contains in 1,000 cc. exactly 40 gm. of anhydrous sulphuric acid, and is therefore normal. 60 gm. of concentrated English sulphuric acid are, therefore, weighed off, diluted with 1,020 cc. of water, and the amount of sulphuric acid in each 20 cc. of this dilute acid is then determined by precipitation with chloride of barium. If, for instance, we have found that 20 cc. contain 0.840 gm. of sulphuric acid, then 1,000 cc. contain 42 gm. Therefore 1,000 cc. of this acid ( $40:1,000=42:x$ ) must be brought to 1,050 cc. by adding 50 cc. of water, in order to obtain an acid which is normal, that is, contains exactly 1 equivalent of  $\text{SO}_4=40$  gm. in the liter. Each cc. of this acid corresponds to  $\frac{1}{1000}$  equivalent of nitrogen  $=0.014$  gm.

*Standard Sodid Hydrate Solution.* This must be equivalent to the sulphuric acid, that is, equal volumes of the two must exactly saturate each other. 20 cc. of the dilute acid, colored.

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\* Heintz, Lehrbuch der Zoochemie, p. 179.

feebly red with tincture of litmus, must be exactly neutralized by 20 cc. of the sodic hydrate solution, free from carbonic acid, so that after the addition of the last drop of the 20 cc. of the sodic hydrate solution, the red color of the sulphuric acid changes to a clear blue. (To prepare such a sodic hydrate solution, see § 76, B, 2.)

C. *The Distilling Apparatus.* This consists of a strong flask of about 100 cc. capacity, whose neck, which is 10 or 12 ctm. long, is closed by a doubly perforated rubber stopper. One hole in the stopper receives a bent glass tube, *e*, which is connected with a Varrentrapp-Will nitrogen apparatus, *f*. A straight glass tube with an opening two mm. in diameter is passed through the other hole and serves to aspirate air through the apparatus after the completion of the combustion, so that the products of combustion may be carried over into the receiver; it therefore extends into the body of the flask nearly to the soda-lime. The outer end of this tube is drawn out to a point and hermetically sealed. After the end of the combustion the point is broken off. The flask is placed in a sand bath of copper plate, and to prevent the deposition of water on that portion of the neck of the flask uncovered by sand, the latter is surrounded by a metallic cover, *c*, which reaches to the stopper. The sand bath is heated by a Bunsen lamp. A good flask suffices for many estimations. The whole arrangement of the apparatus is shown in fig. 38, on the following page.

D. *Process.* 20 cc. of the standard sulphuric acid are introduced into the nitrogen apparatus first, soda-lime freshly ignited is put into the flask, so that the bottom is covered about 1.5 ctm. deep, and then the whole apparatus is put together. When this is accomplished 5 cc. of urine are allowed to flow on to the soda-lime, and the stopper is quickly introduced. The soda-lime must be sufficient in quantity to absorb all of the urine, and it must be uniformly saturated by the urine, so that no layer of fluid remains standing above it. The sand bath is filled with sand up to its edge, so that the metallic cover stands in the sand, and then it is heated as long as any evolution of gas is observable. Heating for half an hour to a red heat is sufficient to expel into the receiver all of the nitrogen in the form of ammonia from 5 cc. of urine. When the liberation of gas has at last wholly ceased, the fine point of the tube *d* is broken

off and air is drawn through the apparatus by means of a rubber tube drawn over the end of the receiver, so that the last traces of ammonia are brought into the sulphuric acid. The combustion is now finished, the nitrogen apparatus is removed, the sulphuric acid is poured into a beaker, thoroughly rinsed

FIG. 38.

out with water, and the non-saturated sulphuric acid titrated back with the equivalent sodic hydrate solution. Each cc. of the sulphuric acid saturated by the ammonia set free indicates 0.014 grm. of nitrogen.

Example :

One cc. = 0.014 grm. of nitrogen. The quantity of urine passed in twenty-four hours = 1200 cc. 5 cc. of urine were used in the analysis. Of the 20 cc. of sulphuric acid contained in the nitrogen apparatus 7.5 cc., as determined by titrating back with the sodic hydrate solution, were saturated, which, therefore, corresponded to  $7.5 \times 0.014$  grm. = 0.1050 grm. nitrogen.

The total quantity of nitrogen eliminated with the urine in twenty-four hours :

$$5 : 0.1050 = 1200 : x = 25.2 \text{ grm.}$$

If a large air pump is available, the following procedure may be adopted, according to Voit:\* Fine ignited quartz sand is placed in a very shallow porcelain capsule of about 8 cm. diameter, a glass cover is then fitted on its broad edge, and the whole apparatus is weighed. 5 cc. of urine are then allowed to flow from a small accurate pipette on to the quartz powder, which must be present in sufficient quantity to completely absorb the fluid, and the apparatus is weighed once more to confirm the measurement. The uncovered dish is now placed under the bell of the air pump together with sulphuric acid, and in a few hours the caked mass becomes so dry that it can be removed in fine powder by scraping from the walls of the dish with the back of a broad knife. The powder thus obtained is mixed with soda-lime and ignited as usual in a combustion tube. The liberated ammonia is collected in standard sulphuric acid, which is best kept in a U-shaped tube, and the quantity determined as given above by titrating back the non-saturated acid.

The estimation of nitrogen is best combined with that of the total solids of the urine according to my method (§ 59, 2). The process is completed as usual, except that in collecting the ammonia a U-shaped tube is used instead of a small flask, and quartz sand instead of bits of glass. The ammonia set free by evaporating the urine and drying the residue is titrated in the usual way, calculated as urea, and the urinary residues found by weighing are added to it. If all of the solid constituents of the urine have thus been determined, the combustion in the tube with soda-lime is performed with the dry residue, but the amount of ammonia already determined, which was formed by the evaporation, etc., from the decomposition of the urea, is added to that last obtained.

The small quantity of nitrites or nitrates which every urine contains does not derange the result, since according to investigations of E. Schulze† small quantities of nitric acid, in the presence of large quantities of organic matter, are likewise completely changed into ammonia on being ignited with soda-lime.

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\* *Zeitschrift f. analyt. Chem.*, Band 7, p. 398.

† *Zeitschrift f. analyt. Chem.*, Band 6, p. 379.

## § 82. ESTIMATION OF THE FAT.

Probably in the very rarest cases would it be of interest to determine quantitatively the fat which occurs in the urine, at most only in very small quantity. If such an estimation, however, is to be undertaken, 20 or 30 cc. of urine are evaporated to dryness on the water bath, and the residue obtained is dried in the air bath for a long time at  $110^{\circ}$ . In order to extract the fat, ether is poured over the residue, thoroughly but carefully mixed with it, and allowed to digest for some time with frequent stirring. The clear ether is then poured off into a light glass tube which has been weighed, fresh ether is added to the residue, and this operation is repeated until the ether takes up nothing more. The ethereal extracts are evaporated in the weighed glass cylinder and the residue which remains is calculated as fat. It must be observed, however, that in this calculation, when the urine contains free lactic acid, the weight of the ethereal residue will be thereby increased, since free lactic acid is also soluble in ether. It is well, therefore, to wash the residue repeatedly with water until it ceases to take up anything, and then to dry and weigh.

## § 83. ESTIMATION OF THE BILIARY ACIDS.

Although even when icterus is very intense, only very small quantities of the biliary acids ever pass into the urine, still, according to Hoppe-Seyler,\* they may be approximately estimated with the polarizing apparatus. The biliary acids are separated from at least 400 or 600 cc. of icteric urine according to the method given by Hoppe-Seyler and described in § 29. The alcoholic solution of the biliary salts, decolorized with animal charcoal if necessary, is next concentrated to a small volume, measured, and then examined with the polarizer according to § 70, 3. Since now the specific rotation of cholate of sodium in alcoholic solution amounts to  $+31.4^{\circ}$ , while that of sugar for medium white light amounts to  $+56$ , the degrees read off on the scale and nonius must be recalculated. The per cent. of cholic acid in the alcoholic solution is found according to the formula

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\* Dessen Handbuch, 8<sup>te</sup> Aufl., p. 286.

$\frac{a}{v} = p$ , and the weight of the cholic acid in the amount of urine subjected to examination is found by the formula  $\frac{a}{100} \cdot \frac{100}{p} = x$ . In this formula  $a$  is the rotation found with an observing tube 0.1 m. long,  $v$  the volume of the alcoholic solution of the cholate of sodium in cubic centimeters, and  $x$  the weight of the cholic acid contained therein. Moreover, if  $v$ , the volume of the alcoholic solution of cholate of sodium, corresponds to 500 cc. of icteric urine,  $\frac{a}{p}$  gives the percentage of the biliary salts in the urine. It is not always the case, as is here assumed, that only cholic acid is contained in the urine, but since the difference in the rotation of glycocholic and cholic acids is only very slight, the error caused thereby falls within the limits of errors of observation, and may, therefore, be disregarded. (Hoppe-Seyler.)

#### § 84. ESTIMATION OF THE INDICAN BY JAFFÉ'S METHOD.\*

*Principle.* If a colorless or feebly-yellow solution of indican is treated with about an equal volume of pure hydrochloric acid, then a few drops of a *saturated* solution of calcic hypochlorite are carefully added, and the mixture shaken, it instantly becomes of an intense blue color, and is rendered cloudy by the separated indigo, which in a few minutes becomes flocculent, and settles completely in a few hours. Human urine is very rarely blue or green, but usually assumes a red or violet shade after the addition of calcic hypochlorite; nevertheless such a specimen after filtration leaves a distinct blue tinge on the filter.

*Process.* 1,000 or 1,500 cc. of urine are rendered alkaline by milk of lime and the phosphates are completely precipitated by chloride of calcium. After standing twelve hours the mixture is filtered and the filtrate and wash water evaporated to a thick syrup, first over a free flame and then on the water bath. At the same time the reaction must be tested from time to time and finally a little carbonate of sodium added. The syrupy residue is warmed several minutes with about 500 cc. of strong alcohol, it is introduced into a beaker, left at rest for twelve or twenty-four hours for the complete separation of everything

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\* Archiv f. d. g. Physiologie, Band 8, p. 448. Zeitschr. f. analyt. Chem., Band 10, p. 126.



precipitable, it is then filtered and the alcohol distilled off. The residue is dissolved in a large quantity of water and precipitated with a very dilute solution of ferric chloride, at the same time avoiding a great excess. The filtrate from the iron precipitate is treated with ammonia, heated to boiling, and after removing the ferric hydrate which has separated, it is evaporated to a volume of from 200 to 250 cc. With this fluid, which, as a rule, must be filtered once more, the estimation of the indigo is carried out as follows: First, the amount of calcic hypochlorite solution necessary to separate the indigo must be ascertained. For this purpose 20 or 40 cc. of the fluid are measured off and gradually diluted with measured quantities of water, until 10 cc. of the mixture treated with an equal volume of hydrochloric acid assume a just perceptible blue color when one drop of a *saturated* solution of calcic hypochlorite is added; the boundary of the reaction has then been reached. It has been found by many experiments that the number of volumes of dilution, which can be added to a solution of indican before the above limit occurs, amounts to about double the number of drops of the calcic hypochlorite solution which are necessary to produce the maximum separation of indigo in 10 cc. of the indican solution. If, then, the above experiment gave the last visible blue color after diluting with water eight times, for every 10 cc. of the undiluted urinary fluid, about four drops of the calcic hypochlorite solution are necessary for the complete decomposition of the indican, after diluting ten times five drops, etc., etc.

We can, therefore, readily determine the necessary quantity of chlorine if we ascertain with a part of the urinary fluid at what dilution the indican reaction just disappears, and in order to be sure, for every 10 cc. we take one or two drops of calcic hypochlorite solution more than half the volumes of dilution. If we have thus found that the limit of the reaction has been reached at a dilution of eight times, we measure off 200 cc. of the urinary fluid, which correspond to a definite volume of the original urine, add an equal volume of hydrochloric acid and then the calculated number of drops of calcic hypochlorite solution drop by drop with constant stirring, in our case, therefore, about 100 drops. We let it stand at least twelve hours to allow the indigo which has separated to deposit completely.

We then filter through a very thick Swedish filter, previously extracted with hydrochloric acid, dried at 150° C. and weighed, and wash successively with cold water, then with hot water, with dilute ammonia, and lastly once more with water, dry at 105° or 110° C., and weigh.

Jaffé found 4·5 to 19·5 mgrm. of indigo in 1,500 cc. of normal urine. Horse's urine contains on the average about twenty-five times as much indigo as human urine. J. Rosenstern\* found a considerable increase of indican in the urine in Addison's disease. The amount of indican in this case amounted to from 53 to 80 mgrm. in 1,000 cc. of urine; it averaged 64·5 mgrm.

#### § 85. ESTIMATION OF THE OXALIC ACID.

For estimating quantitatively the oxalic acid which is present not as a sediment, we may follow the same method which I have given above, § 45, C, for detecting oxalic acid in urine which has not deposited a sediment. After standing twenty-four hours, the separated calcic oxalate is transferred to a small filter, the weight of whose ash is known, it is washed, dried, and the calcic oxalate transformed by a strong red heat into caustic lime. The amount of caustic lime obtained multiplied by 1·6071 gives the corresponding amount of oxalic acid =  $C_2H_2O_4$  [ $C_4H_2O_6$ ].

The method given by O. Schultzen† for the same purpose gives less reliable results, since, as Salkowski‡ states, Senator has proved that calcic sulphate is precipitated at the same time by this procedure.

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\* Virchow's Archiv, Band 56, p. 27.

† Reichert u. Dubois-Reymond's Archiv, 1869, p. 718.

‡ Archiv für patholog. Anatom., etc., Band 50.

## DIVISION THIRD.

### SYSTEMATIC COURSE OF QUALITATIVE AND QUANTITATIVE ANALYSIS OF URINE.

#### I. QUALITATIVE ANALYSIS.

##### § 86.

THE qualitative analysis of a urine may naturally be performed in two different ways, according as we wish to ascertain the presence or absence of any normal or abnormal constituent of the urine, or to obtain a complete qualitative representation of the urine passed at any given time. In the first case a few tests are sufficient, as a rule, to obtain our object; but in the second it is well to follow a plan which includes all of the individual substances. The following section may be regarded as such a plan, in which consideration is taken of all of the normal constituents of the urine, as well as of the most important and most common abnormal constituents; while with regard to those which are more rarely met with, and those which require very large quantities of urine for their investigation, I must refer to the sections in Division First, in which they are treated. Moreover, since I have already described at length in Division First the processes for detecting all of the constituents of the urine, it will suffice here to give merely a schedule of the processes to be carried out, and with regard to their special performance to refer to the former sections.

#### A. SYSTEMATIC PROCESS FOR DETECTING THE SOLUBLE CONSTITUENTS.

##### § 87.

1. The reaction is tested with litmus paper.
  - a. If the urine is acid and contains no sediment, we proceed as described in 2.

b. If the urine is acid and contains a sediment, we allow it to settle, pour off the clear urine, filter if necessary, and test it according to 2.

The sediment is to be examined microscopically according to § 88.

c. The urine is neutral or alkaline. In this case there is usually a sediment in it; the sediment is tested according to § 88, and the filtered urine according to 2.

2. A small portion of the urine rendered acid, if it is not already so, by a drop of acetic acid, is heated to boiling. If a coagulum is formed which does not disappear after the addition of nitric acid, it consists of albumen. We then separate all of the albumen from a larger quantity of urine (500 or 600 cc.) by boiling (§ 23, E), filter, and treat the filtrate according to 3.

The reaction with nitric acid serves as a confirmatory test (§ 23, C, 9), also the test with carbolic acid by the method of Méhu, page 97.

If the quantity of albumen is very small, the nitric acid is very carefully covered with a layer of the urine to be tested; mere traces of albumen produce a turbidity in the form of a sharply defined zone at the point of junction of the two fluids (§ 23, E), at the end.

The resulting coagulum is either:

- a. *White*, when it consists of pure albumen;
- b. *Greenish*, when we have reason to suspect biliary matters, especially if the urine itself was deeply tinged (§ 28);
- c. *Brownish red*, when we may suspect the presence of blood; we therefore test the sediment carefully, according to § 88, and test the original urine with the spectroscope according to § 51, B, 1 and 2. The dried coagulum is treated with alcohol and a few drops of sulphuric acid. If the fluid after filtration is more or less red, it is first tested for hæmatin with the spectroscope (§ 51, B, 2), then evaporated to dryness and ignited. The residue is heated with water to which a little hydrochloric acid has been added, it is filtered and the solution tested with sulphocyanide of potassium. The occurrence of a red color indicates the presence of iron.

Hæmatin in solution is tested by Heller's test (§ 51, B, 2, c). A specimen of the urine is heated to boiling, concentrated po-

tassic hydrate is added and the color of the fluid observed, as well as the color of the earthy phosphates which are separated in flocculi after standing for a short time.

Another specimen is treated with ammonia, then with tannin solution, and lastly with acetic acid until the reaction is distinctly acid. The precipitate which may occur is treated exactly according to § 51, B, 2, d, and finally used for the production of hæmin crystals which are so characteristic of blood pigment.

3. About 600 or 800 cc. of clear urine or of urine separated from its sediment or albumen coagulum by filtration are evaporated on the water bath to the consistence of a thick syrup, and the residue obtained is divided into two portions ( $\frac{1}{3}$  and  $\frac{2}{3}$ ).

a. One-third of this residue is extracted with strong alcohol, the undissolved portion is allowed to settle, the solution is filtered, the residue again washed once or twice with strong alcohol, and the solution tested as follows (aa), and the residue according to c.

aa. A small quantity of the alcoholic solution is evaporated nearly to dryness on the water bath, and the residue tested for urea by adding nitric or oxalic acids (§ 2, D, 9, a and b).

bb. The greater part of the alcoholic solution is treated with a few drops of milk of lime, and then with a solution of chloride of calcium as long as any precipitate is produced by it. The filtrate is evaporated on the water bath to 10 or 12 cc., introduced into a beaker, and after cooling treated with  $\frac{1}{2}$  cc. of an alcoholic solution of chloride of zinc. After being well shaken the mixture soon becomes cloudy and *kreatinin-chloride of zinc* is formed. The precipitate collected after a few hours is tested microscopically according to § 3, C, 1.

Large quantities of kreatinin may be easily obtained as described in § 3, D, and § 5, D, 2.

b. Two-thirds of the residue are slightly acidulated with hydrochloric acid, rubbed up with powdered sulphate of barium, and then extracted with alcohol. The alcoholic solution is used for testing for *hippuric acid*, as described in § 8, E.

The crystals obtained are examined microscopically (Plate I, fig. 1), and, as far as the material serves, chemically also (§ 8, D, 7).

The detection of hippuric acid according to § 8, E, 2, is very easy and certain. The kreatinin can be precipitated by chloride of zinc solution from the urinary extract after exhaustion with ether, after it has been exactly neutralized with sodic hydrate solution and diluted with 30 cc. of absolute alcohol. The saline mass precipitated from the evaporated urine by absolute alcohol is tested for any succinic acid which may be present, as described in § 8, E, 2.

c. The residue which has been obtained by treating with alcohol, according to a, is covered with dilute hydrochloric acid (one part of hydrochloric acid and six parts of water) in the evaporating dish, and the undissolved portion separated by a small filter.

aa. The hydrochloric acid solution contains the *earthy phosphates* and other salts; the former are precipitated by neutralizing the solution with ammonia.

bb. The residue which is left contains *mucus* and *uric acid*. After washing it, the filter is perforated and the residue washed, by means of a wash bottle, into a small test tube, two or three drops of sodic hydrate solution are added, it is heated and filtered.

$\alpha$ . The undissolved residue is *mucus*.

$\beta$ . The filtrate contains the *uric acid*, which when treated with hydrochloric acid separates in crystals which are examined under the microscope (§ 6, c). The remainder is dissolved in nitric acid, carefully evaporated to dryness and exposed to ammonia, as mentioned in § 6, E, 1, a. If a purple violet color is formed, which becomes purple blue on adding potassic hydrate, it is absolute proof of the presence of uric acid.

If the residue is immediately treated with sodic hydrate or potassic hydrate instead of with ammonia, a purple violet solution results, which becomes paler on heating, and at last wholly loses its beautiful color. (Distinction from xanthin.)

The uric acid is easily obtained in finely formed crystals, if 200 cc. of urine are treated with 5 cc. of hydrochloric acid, and left at rest for twelve hours (§ 6, E, 2).

d. The alcoholic extract of a large quantity of urine is required in testing for lactic acid (§ 30, C).

e. The method described in § 5, D, for the simultaneous de-

tection of kreatinin, xanthin, and urea, gives with certainty the desired result.

f. Oxaluric acid can only be detected by using very large quantities of urine (§ 7, E).

4. Three or four cc. of fuming hydrochloric acid are mixed in a test tube with twenty or twenty-four drops of the urine to be tested. If *uroxanthin* (indican) is present, the mixture in a very short time becomes colored a red violet or intense blue. If on account of the minute quantity of *uroxanthin* present, the reaction does not take place, it may often be produced by adding a few drops of strong nitric acid (§ 10, IV. c). The test with calcic hypochlorite by Jaffé's method (§ 40, IV. c, 2) is also very delicate.

In testing for *urobilin* we proceed exactly according to § 10, I. c.

5. If the urine is colored more or less deeply brown or green, etc., if it foams on being shaken, and if a piece of filter paper is colored yellow or green on being dipped into it, we have reason to test for *bile*.

a. A small quantity of urine is poured into a conical-shaped glass, and nitric acid containing nitrous acid is added, drop by drop, without shaking. If in the lower part of the fluid a color is formed which passes through green, blue, violet to red, and lastly into yellow, the presence of the bile pigments is indicated.

If there are only slight traces of bile pigment present, the nitric acid is to be carefully covered with a layer of the urine to be tested, or the bile pigment is to be first separated with chloroform (§ 28, D, 1 and 2).

b. In testing for the *biliary acids*, 400 or 600 cc. are evaporated on the water bath and the alcoholic extract employed. For the process see § 29, under Detection. Pettenkofer's test, as stated there, is performed in a porcelain dish.

If the reaction mentioned does not occur, but the urine betrays the presence of biliary pigment by its color, this may be choletelin, the last yellow product which results from the action of nitric acid, etc., on bilirubin. In this case we test according to § 28, D, 3, and confirm by the spectroscopic test.

To detect the biliary acids in normal urine they are to be separated with chloroform according to Dragendorff's method (§ 29, Detection, 3).

6. If there is any reason to test for sugar :

a. Fifteen or twenty drops of the urine in question are diluted with 4 or 5 cc. of water,  $\frac{1}{2}$  cc. of sodic hydrate is added, and then a very dilute solution of sulphate of copper is dropped in. If *sugar* is present, red suboxide of copper separates immediately on heating, but in the cold only after standing a long time (§ 25, D, 7).

If the reduction is not well marked, if the suboxide of copper remains in solution, the urine is filtered through animal charcoal until it is completely decolorized, and is then used for the above test.

The following serve as confirmatory tests :

$\alpha$ . The potash test. § 25, D, 5.

$\beta$ . The bismuth test. § 25, D, 10.

$\gamma$ . The indigo reduction test. § 25, D, 6.

$\delta$ . The silver reduction. § 25, D, 9.

$\epsilon$ . The fermentation test. § 25, D, 8.

b. If the reactions given under  $\alpha$  are not decisive, if, indeed, only traces of *sugar* are present, it must first be separated in a pure form, according to § 25, E, II., and the solution obtained be finally used for the above reactions.

7. If the urine has the odor of sulphuretted hydrogen, if it colors brown or black a piece of paper moistened with basic acetate of lead (§ 34), the presence of sulphuretted hydrogen is indicated.

8. To test the urine for inorganic substances, a portion (80 or 100 cc.) should be evaporated to dryness and the residue ignited, as described in § 60. The ash is extracted with water, filtered, and tested as follows :

a. A small portion of it is rendered acid with hydrochloric acid, and chloride of barium is added; a white pulverulent precipitate indicates the presence of *sulphuric acid*.

b. A second portion is made acid with nitric acid, and a solution of nitrate of silver is added. A white curdy precipitate indicates *chlorine*.

c. A third portion is treated with acetate of sodium, acetic acid, and a few drops of uranium solution; a yellowish-white gelatinous precipitate indicates *phosphoric acid*.

d. The rest of the aqueous solution is evaporated to dryness, and a small portion of the saline mass heated to redness on a



platinum wire in the inner flame of the blowpipe ; a yellowish color of the outer part of the flame indicates *sodium*.

e. The rest of the saline mass, obtained as indicated in d is dissolved in a few drops of water, and platonic chloride added. A yellow crystalline precipitate indicates *potassium*.

To test for *lithium*, which readily passes into the urine on being taken internally, the dried saline mass obtained in d is next repeatedly treated with absolute alcohol, the alcoholic solution is evaporated to dryness, and the residue tested with the spectroscope. Salts of lithium give a beautiful bright red line between the Fraunhofer lines B and C.

9. The residue of 8, treated with water, is heated with hydrochloric acid, filtered, washed, and tested as follows :

a. A small portion of the solution is boiled with a drop of nitric acid, and sulphocyanide of potassium is added ; if a red color is produced *iron* is present.

b. The rest is treated with an excess of acetate of sodium and tested for *calcium* with oxalate of ammonium.

c. All of the calcium is precipitated, the fluid separated by filtration, and ammonia added to the filtrate. A white crystalline precipitate of ammonio-magnesian phosphate indicates the presence of *magnesium*.

Most of these tests (8 and 9) can be performed with the original urine, filtered if necessary, yet they give clearer and more distinct results when the tests are applied to the ash.

10. In testing for ammoniacal salts, 50 or 100 cc. of urine are treated with milk of lime in a flask, in the body of which a piece of moistened turmeric paper is suspended from the stopper. If ammonium salts are present the paper quickly becomes brown (§ 19).

11. The possible presence of iodine is best detected by distillation with sulphuric acid according to § 71, C. The distillate obtained, after removing the sulphurous acid, may be tested for iodine with a few drops of starch paste, and the careful addition of chlorine water, or, better still, of red fuming nitric acid instead of with the palladium solution (§ 71, C). The smallest traces of iodine will give rise to the formation of blue iodide of starch.

For other methods of testing for bromine and iodine see § 56, I. C, 8, 9, and § 71, 2.

12. In testing for the volatile fatty acids and carbolic acid

large quantities of urine are necessary, and the analysis should not be undertaken with less than 50 or 60 pounds of urine. For the methods see § 9 and § 31.

13. Benzoic acid is only found in decomposed alkaline urine. 6 or 8 pounds are requisite to detect it satisfactorily. Benzoic acid is best found in fermented diabetic urine. To separate it we must proceed exactly as is described in § 32, D.

14. Inosite has hitherto only been found in cases of Bright's disease and diabetes (§ 27, D).

15. Allantoin. See § 35, E.

16. To test for xanthin we require large quantities of urine (§ 5, D).

17. Leucin and tyrosin have been found in acute atrophy of the liver, typhoid fever, small-pox, etc. It is probable that the urine then contains, in addition to these substances, valerianic acid also. For the methods of detecting see § 37, E.

18. For nitric acid, nitrous acid, and peroxide of hydrogen, we test according to § 21 and § 22.

19. We test for oxymandel acid as in § 38; it has thus far only been found in acute atrophy of the liver.

20. We test for brencatechin according to § 39.

21. For acetone we test according to § 41.

## II. RECOGNITION OF SEDIMENTS UNDER THE MICROSCOPE.

### § 88.

If we wish to examine the sediment of a urine, it is necessary to know first whether the urine in question is fresh, or whether it has already stood a long time, and the changes which are caused by fermentation have commenced. We therefore test its reaction, let the sediment subside completely in a closed vessel, pour off the supernatant fluid, which must be examined according to § 87, and place a drop of the sediment on a glass slide. If the quantity of urine is small, it is poured into a champagne glass and left at rest until the fluid has become clear. The supernatant fluid is then removed with a siphon, and a drop of the sediment which has collected in the apex of the glass is placed on a glass slide. If the quantity of urine is large, that of twenty-four hours, it is first allowed to

settle in a covered vessel, the clear fluid is then drawn off with a siphon, the rest is put into a champagne glass and again allowed to settle, and we then proceed as before. The drop on the slide is next covered with a covering glass and systematically examined, by beginning on one side of the specimen and pushing it back and forth under the objective until every point of it has been in the field of vision. When we have examined one specimen, a second is taken, etc.; it is advisable, also, to take specimens from different layers of the sediment, since some bodies sink more rapidly than others. When it is possible, the microscopic examination should be made twice; first, as soon as possible after the urine has been passed, and again when the urine has stood twenty-four hours. Calcic oxalate, for example, is not usually found in freshly passed urine, but first makes its appearance after the lapse of a few hours. We increase our magnifying power from 50 or 80 diameters up to 300 and 400. If the urine has been filtered to separate the sediment and the latter is removed from the filter by scraping, we must be careful to avoid regarding paper fibres, etc., as constituents of the sediment.

A. *The Urine has an Acid Reaction.*

1. *The whole sediment is amorphous*, arranged partly in irregular heaps, or in branched mossy rows of very small granules. A drop is heated on a glass slide.

a. If complete solution takes place it indicates the presence of *urates*. (Plate II., fig. 1 and 2.) After it has cooled, a drop of hydrochloric acid is added, and it is allowed to stand for a quarter or half an hour; the formation of rhombic tables of uric acid proves the presence of this substance. (Plate I.; fig. 2.)

In most cases this sediment consists of a mixture of acid urates, and is distinguished by a more or less red color. (Plate II., fig. 1 and 2.) The sediment is tested chemically, according to § 44.

These sediments are very frequently accompanied by uric acid and calcic oxalate crystals. (Plate I., fig. 3; and Plate II., fig. 4.)

b. If the sediment does not dissolve on being heated, but does dissolve in acetic acid without effervescence, *calcic phosphate* is probably present. We confirm chemically as in § 46.

c. If we find in the amorphous sediment small, highly re-

fractive, silvery, shining drops, which are soluble in ether, they indicate the presence of *fat* (§ 33).

2. *The Sediment contains well-formed Crystals.*

a. Small, shining, perfectly transparent, highly refractive, envelope-shaped, rhombic octahedra, insoluble in acetic acid, are *calcic oxalate* crystals. (Plate I., fig. 3; Plate II., fig. 4, § 45.) (300 or 400 diameters.)

b. Four-sided tables, or six-sided plates of rhombic shape, from which spindle- or barrel-shaped crystals are formed by the rounding of their obtuse angles, are *uric acid*. These sediments are usually more or less colored. (Plate I., fig. 2 and 3; Plate II., fig. 4; Plate III., fig. 1, § 6, C.)

We can detect it chemically by the murexid test (§ 6, E, 1, a).

If there is doubt about some of the forms, the sediment is dissolved in a drop of sodic hydrate solution on a glass slide, a drop of hydrochloric acid is added, and the forms which now appear are observed.

Just at the commencement of the alkaline fermentation the uric acid crystals, which are more or less dissolved, are frequently studded with groups of prismatic crystals consisting of *urate of sodium*, upon which again are deposited concentrically striped spheres of *urate of ammonium*. Not unfrequently solitary crystals of calcic oxalate are found at this time also.

c. Regular six-sided tables, which dissolve in hydrochloric acid and ammonia, char and burn on heating, and which give a precipitate of sulphide of lead when boiled with a solution of lead oxide in caustic soda, consist of *cystin*. (§ 47, Plate III., fig. 4.)

The test with nitroprussiate of sodium for cystin is very delicate (§ 47, C, 8).

d. Prismatic, often wedged-shaped crystals which sometimes lie singly, and sometimes with their pointed ends so placed together that they form a more or less complete circle, consist of *crystallized calcic phosphate* (§ 46, 2).

These crystals are quite soluble in acetic acid.

e. Heavy, greenish-brown, spherical granules with a stellate crystalline structure may consist of *tyrosin*. Saturating its ammoniacal solution with acetic acid precipitates characteristic groups of long shining needles (§ 37, B).

To confirm its presence the different chemical tests are applied, according to § 37, C, 2, 3, 4.

Urine containing tyrosin very frequently contains bile pigments also.

f. *Hippuric acid* is very rarely met with as a sediment in the form of needles or rhombic prisms which are readily soluble in hot water (§ 8, B, D).

### 3. *The Sediment contains Organized Substances.*

a. Spiral bands which consist of fine points and granules arranged in rows are *mucous coagula*, and are often accompanied by urates. (Plate II, fig. 2, § 50.)

These must not be confounded with so-called casts. (See e.) (§ 53; Plate I, fig. 4, 5, 6.)

b. Small, strongly contracted and granular bodies, which are usually united by their edges into large groups like a coat of mail, are *mucous corpuscles*. (§ 50, Plate II, fig. 3.)

c. Circular, slightly biconcave disks, which usually appear yellow, become swollen strongly on the addition of acetic acid, and are more less quickly dissolved by it, are *blood corpuscles*. (Plate III, fig. 1 and 2.)

We should pay special regard to the swollen spherical forms, as well as to the distorted, angular, and crenated ones (§ 51).

When blood is present the urine contains albumen.

d. Round, pale, faintly granular cells of different sizes, which become swollen considerably by acetic acid, lose their granular surface and present nuclei of different forms and groupings, are *pus corpuscles*. (§ 52, Plate III, fig. 3.) We cannot distinguish these bodies chemically or microscopically from mucous corpuscles. (Plate II, fig. 3.)

When pus is present, the urine contains albumen.

The deposited sediment, when pus is present, is changed to a thick, tenacious, ropy mass by potassic or sodic hydrate solution. (Donné's pus test, § 52, B.)

e. Cylindrical bodies often studded with blood and pus corpuscles and accompanied by epithelial cells and mucous corpuscles are so-called *renal casts*. (§ 53, Plate I, fig. 4, 5, and 6.)

aa. Cylindrical casts whose round nucleated cells are distinctly visible through a fine molecular mass are *epithelial casts of the tubes of Bellini*. (Plate I, fig. 4.)

These forms are usually accompanied by free club-shaped,

caudate or spindle-shaped nucleated epithelial cells from the ureters, pelvis, and calices of the kidney. (Plate I., fig. 4.)

bb. Solid cylinders of a granular cloudy appearance are the so-called *granular renal casts*. (Plate I., fig. 6.)

These cylinders often contain blood and pus corpuscles as well as fat drops and granules of fat, also crystals of calcic oxalate and single epithelial cells.

The sediment, moreover, frequently contains blood and pus corpuscles as well as the free epithelial cells mentioned under aa. (Plate I., fig. 6.)

cc. Solid cylinders of very pale transparent character, so that we can frequently distinguish them from the surrounding fluid only with great difficulty, are the so-called *hyaline renal casts*. (Plate I., fig. 5.)

Their recognition is rendered easier if a solution of iodine in iodide of potassium or a solution of fuchsin is added to the specimen whereby these bodies assume a yellow or red color.

We frequently find intermediate forms between bb and cc, by the hyaline casts assuming a more or less granular appearance, owing to overlying fat drops, pus corpuscles, and finely granular masses.

*Every specimen of urine containing albumen must be carefully examined for these different bodies.* We should choose a power of 180 or 200 diameters.

f. *Epithelial cells* of different forms according to their source.

aa. Pavement epithelium. Roundish, long, or polygonal nucleated cells from the large and small labia, the vagina, the female urethra, bladder, pelvis of the kidney, and calices. (Plate I., fig. 4, 5, 6; Plate II., fig. 1, § 50, 2.)

bb. Cylindrical and oval epithelium from the lower layer of the mucous membrane of the bladder, etc.

cc. Ciliated epithelium from the uterus.

The addition of a solution of iodine in iodide of potassium or of a solution of fuchsin renders all of these forms more distinctly visible under the microscope.

g. *Fermentation spores* and *mycelium* accompany sediments of urates, free uric acid, and calcic oxalate in commencing acid fermentation, but occur especially in diabetic urine which has undergone fermentation.

aa. The fermentation spores are small nucleated cells which

increase by budding, and thus form simple or branched rows. (Plate II., fig. 1, 2, 4.)

bb. Mycelium often forms a thick network which may cover the whole field. (See page 189, fig. 5.)

h. Short fine rods which move briskly here and there or with a serpentine motion are *vibriones*; they are commonly seen in feebly acid or alkaline urine with a high power (§ 55).

i. *Spermatozoa* are recognized by their tadpole-like shape (§ 54).

k. *Masses of Cancer*. (Plate III., fig. 5 and 6.)

l. *Sarcina ventriculi*, *Goodsir*. Very rare. Its characteristic form does not admit of its being easily mistaken. (Page 189, fig. 6.)

B. *The Urine is Alkaline*.

1. *The Sediment contains Crystals*.

a. Combinations of the vertical rhombic prism, which resemble a coffin lid in shape, are soluble in acetic acid, and on heating with a solution of sodic hydrate evolve ammonia, are crystals of *ammonio-magnesian phosphate*. (§ 46, 1; Plate II., fig. 3 and 5.)

If calcic oxalate should occur with these, the sediment is treated with a drop of acetic acid on a glass slide; the crystals of magnesium phosphate will dissolve, while the calcic oxalate will remain behind in its envelope-shaped crystalline form.

b. Spherical opaque masses which appear like thorn apples with peculiar, prominent, fine points, but also in glandular conglomerations consisting of small, curved, club-shaped bodies, are *urate of ammonium*. (§ 44, 3; Plate II., fig. 5.)

2. *The Sediment contains Amorphous Masses*.

In an alkaline urine these almost always consist only of calcic phosphate (§ 46, 2).

3. *The Sediment contains Organized Bodies*.

Besides mucus, blood and pus corpuscles, etc., we find here fermentation spores and mycelium, infusoria, and confervæ (§ 55, page 189, fig. 5). In an alkaline urine pus is changed to a ropy slimy mass (§ 52, B).

## § 89. PRESERVATION OF URINARY SEDIMENTS.

As in many cases it may be of interest to preserve urinary sediments as microscopic objects, the following short introduc-



tion for that purpose may find mention here. First of all it is necessary to separate the sediment from the urinary fluid, as the urine soon undergoes decomposition, and, therefore, organized bodies especially are easily destroyed. The sediment is, therefore, allowed to settle in a champagne glass, the urine as far as possible is drawn off with a siphon, and the sediment is then washed three or four times by decantation with the preservative fluid, in which we wish to enclose it later. Two methods are open to us: we may either put the washed sediment into a small bottle, fill it with the preservative fluid, and write the contents on a label, or we may place the sediment on a glass slide and preserve it as a finished preparation under a covering glass hermetically sealed.

Of the different preservative fluids proposed for this purpose glycerine solution,\* creosote and wood spirit solution,† dilute alcohol,‡ Farrant's fluid,§ etc., are best fitted for the various epithelial cells, renal casts, pus and mucous corpuscles, spores, uric acid, urates, calcic oxalate, etc.¶ Ammonio-magnesian phosphate is best preserved in water to which a little ammonia has been added. Very dilute acetic acid is selected for cystin. Crystalline sediments, with the exception of ammonio-magnesian phosphate and calcic oxalate, may be preserved in Canada balsam, but they must first be very completely

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\* Glycerine solution is obtained by diluting commercial, thick, syrupy glycerine with equal parts of camphor water. It forms an excellent preserving fluid.

† Creosote and wood spirit solution is obtained as follows: Three drams of creosote are mixed in a mortar with six ounces of wood spirit, and powdered chalk is added until the whole forms a thin pulp, which is then diluted with sixty-four ounces of water while being rubbed well together. A few pieces of camphor may also be added. The mixture is then allowed to stand two or three weeks in a closely covered glass, being frequently stirred. At last the clear fluid is poured off, filtered, and preserved in a well-stoppered bottle.

‡ Rectified spirit is diluted with from two to eight times its quantity of water. It is less suitable for microscopic preparations, since it is difficult to hermetically seal preparations preserved in alcohol.

§ A mixture of equal volumes of very thick mucilage, glycerine, and a cold saturated solution of arsenious acid.

¶ [*Reviser's Note.*—An excellent preservative fluid for the organized sediments is a solution of the acetate of potassium to which a little carbolic acid has been added. The acetate of potassium solution should have a sp. gr. of between 1.050 and 1.060, and should contain 4 to 5 cc. of deliquesced carbolic acid to the liter of solution.]



washed and carefully dried. The following procedure is the simplest: The well-washed sediment is placed on a glass slide and allowed to dry thoroughly in the sun or over sulphuric acid; it is then moistened with a drop of oil of turpentine, the greater part of which is again allowed to evaporate. A drop of Canada balsam is now placed upon it, it is gently warmed, any air bubbles present are removed with a needle, and it is covered with a previously warmed covering glass. By careful pressure the excess of balsam is forced out, and after a few days it dries and forms a perfectly tight border around the covering glass. For still greater security the edge may be covered with asphalt varnish, which is an article of commerce, and may be readily applied with a camel's-hair brush.

To preserve sediments in a fluid we proceed as follows: A drop of the sediment suspended in the preservative is placed on a glass slide and a covering glass previously breathed upon is carefully placed over it with a pair of forceps, taking care that no air bubbles are included under it. The excess of fluid is then removed by gentle pressure, carefully absorbed by filter paper, and the preparation laid aside a few minutes to allow the very last of the fluid to evaporate. We now place the preparation under the microscope to see that everything is right, and then proceed to hermetically seal it. The covering glass is first fastened to the slide by means of wax. The wick of a thin wax taper is sharpened into a chisel shape, then heated to the melting point over a spirit lamp, but not until it burns, and then, while the wick is held horizontally, it is quickly drawn along the edge of the covering glass. In this process drops of wax must not be allowed to fall off, but only just enough to perfectly fill the furrow between the covering glass and glass slide, and the whole border of wax should not be more than 2 mm. wide. With a little practice the wax may be as evenly laid on as fluid with a brush. When the wax bedding is finished, it is covered with asphalt varnish, which may be easily applied with a hair pencil, so as to cover the wax bed 2 mm. beyond each edge; we have thus a border about 6 mm. broad, which surrounds the preparation. In applying the asphalt we must proceed with care, and see that we cover all of the corners and edges well, and that no air bubbles have been included anywhere; this we can best determine by means of a

hand lens. We should be especially careful not to make this first layer of asphalt too thick, since it then hardens only on the surface, still remaining fluid beneath and easily being drawn under the covering glass and thus spoiling the preparation. I have lost many preparations in this way. If after twenty-four hours the first layer of varnish has become solid, a second thicker one is applied over it, when the preparation may be labelled.

The glass slides should be 48 mm. long and 28 mm. broad. Protectors, 10 mm. broad, should be glued on to both ends with mucilage or silicate of potassium varnish, and at the same time they should carry the labels. These protectors are to be recommended very highly, since the covering glass is then never in danger when the preparations are packed one upon another. The finished preparations should never be placed on their edge, since they then more readily become leaky, but they should always be laid flat in a box lined with cloth. The process described here is applicable not only to urinary sediments, but also to many other microscopic preparations.\*

### III. QUANTITATIVE ANALYSIS.

#### § 90.

If we have obtained a satisfactory knowledge of the urine under examination qualitatively, according to § 87 and § 88, we proceed to determine the constituents quantitatively. Unfortunately, however, we do not yet possess simple and accurate methods for determining quantitatively all of the bodies which occur, therefore we must content ourselves with estimating the most important of the normal and abnormal constituents.

#### 1. *Estimation of the Quantity of Urine Passed in a Given Time* (§ 57).

According to the purpose which we have in view, we either determine the amount of urine for twenty-four hours, or for a shorter time. The amount should be stated in cubic centimeters (§ 57).

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\* Very thorough instruction in this subject can be found in Welker's *Aufbewahrung microscopischer Objecte*, Giessen, 1856; also in Reinhard's *Das Microscop und sein Gebrauch für den Arzt*, Leipzig and Heidelberg.

2. *Estimation of the Specific Gravity* (§ 58).

In most cases the determination of the sp. gr. can be made with the urinometer, § 58, 1. But if greater accuracy is desirable, we use the method of weighing, § 58, 2 and 3.

The statement of the sp. gr. is rendered more complete by a simultaneous statement of the temperature of the urine.

3. *Determination of the Water and of the Total Solids* (§ 59).

10 or 15 cc. of urine are evaporated on the water bath in a weighed porcelain crucible exactly according to § 59, and the residue is dried in the air bath at 100° until it no longer loses weight. After subtracting the weight of the crucible we obtain the amount of solid constituents, and if we subtract this from the amount of urine taken, it gives us the amount of water in the urine.

Much more accurate results are obtained when the evaporation of the urine is performed in the apparatus figured in § 59, 2, fig. 17. The ammonia which is liberated by the decomposition of the urea when the urine is evaporated is calculated as urea, and this is added to the residue found by weighing.

4. *Determination of the Non-volatile Salts* (§ 60).

10 cc. of urine are evaporated to dryness in a weighed platinum crucible, and the residue is ignited as described in § 60.

If we wish to determine the constituents which are soluble in water separately from those which are insoluble, we boil the weighed residue with water, filter, wash, evaporate the aqueous extract to dryness in a weighed platinum crucible, ignite gently, and weigh. The weight of salts soluble in water subtracted from the whole quantity of non-volatile bodies found gives as the difference the amount of salts insoluble in water.

5. *Determination of the Coloring Matter by Vogel's Method.*

This process is carried out exactly as described in § 61.

6. *Determination of the Urea.*

A. *The Urine contains no Albumen.*

50 cc. of urine are mixed with 25 cc. of a cold saturated solution of caustic baryta and nitrate of barium (§ 65, B, 3), and the resulting precipitate filtered through a dry filter.

The filtrate obtained is divided into two portions.

a. One portion is made very feebly acid with dilute nitric acid, 15 cc. are measured off with a pipette, corresponding to 10 cc. of urine, and it is treated with a standard solution of

mercuric nitrate from a Mohr burette drop by drop until a distinct, permanent, whitish cloudiness appears. The number of cc. used up to this point gives the correction for chloride of sodium and is subtracted from the number of cc. of mercury solution used under b (§ 65, D, 3, at the end). (Rautenberg's method.)

b. The second portion of the filtrate is not rendered acid, but 15 cc.=10 cc. of urine are also measured off with a pipette, and the urea is determined by the standard solution of mercuric nitrate, § 65, C. This is added from a burette until a drop of the mixture saturated with carbonate of sodium on a watch glass gives a distinct yellow color. If the mixture remains white, there is still some uncombined urea present, and more mercuric solution must be added. The result of the first should be confirmed by a second test; every cubic centimeter of the mercuric solution used, after subtracting those obtained under a, corresponds to 10 mgrm. of urea.

For the principle, preparation of the solutions, etc., see § 65.

*Corrections.*

aa. *The Urine contains more than two per cent. of Urea.*

If more than 30 cc. of the mercuric solution have been employed for the 15 cc. of the urine mixture, before testing the mixture with carbonate of sodium, we must add a quantity of water equal to half that of the mercuric solution in excess of 30 cc. which has been used (§ 65, D, 1).

bb. *The Urine contains less than two per cent. of Urea.*

If less than 30 cc. of the mercuric solution have been used for the 15 cc. of the urine mixture, 0.1 cc. must be subtracted for every 5 cc. less than 30 cc. which have been used, and the remainder calculated for urea (§ 65, D, 2).

cc. *The Urine contains one to one and a half per cent. of Chloride of Sodium.*

If we wish to obtain perfectly accurate results, the chlorine must first be removed by a standard solution of nitrate of silver. The urea in the filtrate is then determined by the mercuric solution as usual, account being taken of the dilution which has been caused by the nitrate of silver solution (bb). (§ 65, D, 3.)

The method of Rautenberg described in § 65, D, 3, at the end, gives nearly as accurate results. (See page 239.)

dd. *The Urine contains carbonate of ammonium* (§ 65, D, 5, b).

A measured volume of urine, which has been completely precipitated by baryta solution, is subjected to distillation, and the ammonia which is set free is received in a measured volume of standard sulphuric acid (§ 65, D, 5, b). Each cubic centimeter of the saturated acid corresponds to 11.32 mgrm. of ammonia or 20 mgrm. of urea.

The undecomposed urea is determined as usual in the residue freed from ammonium salts.

B. *The Urine contains Albumen.*

The albumen in a definite quantity of urine is coagulated as in § 65, D, 4, filtered, and the urea, after precipitating the phosphates with baryta solution, determined as usual (§ 65, C).

For clinical purposes the method of Knop-Hüfner (§ 65), with hypobromite of sodium, is also to be highly recommended.

7. *Determination of the Chlorine* (§ 66).

5 or 10 cc. of urine are treated with 1 or 2 grm. of pure nitre, evaporated to dryness in a platinum evaporating dish, and carefully heated until the organic bodies are completely decomposed. The white saline residue is dissolved in water, accurately neutralized with nitric acid, and the chlorine estimated with the solution of nitrate of silver according to § 66, C.

Each cc. of the silver solution corresponds to 6.065 mgrm. of chlorine or 10 mgrm. of chloride of sodium.

8. *Determination of the Phosphoric Acid* (§ 67).

a. *Estimation of the Total Amount.* 50 cc. of urine are treated with 5 cc. of an acid solution of acetate of sodium, heated on the water bath, and then the phosphoric acid is determined with a standard solution of acetate of uranium. During the addition it is frequently tested by adding a drop of the mixture to a solution of ferrocyanide of potassium in the manner recommended in § 67, C, until a slight excess of uranium is indicated by a faint red color. Each cubic centimeter of the uranium solution used corresponds to 5 mgrm. of phosphoric acid (§ 67, C, a).

b. *Determination of the Phosphoric Acid combined with Alkalies.* 50 cc. of urine are rendered alkaline with ammonia, the earthy phosphates are filtered off after a few hours, the precipitate is washed, and the phosphoric acid is estimated in the whole filtrate

after adding 5 cc. of the acetate of sodium solution as explained in a.

Each cubic centimeter of the uranium solution which was used indicates 5 mgrm. of phosphoric acid which were in combination with the alkalies. The quantity thus obtained subtracted from the whole quantity previously determined gives as a difference the phosphoric acid combined with the earths.

9. *Determination of the Free Acids* (§ 68).

50 cc. of urine are treated drop by drop with a solution of sodic hydrate standardized with pure oxalic acid, until the acid reaction has wholly disappeared and a drop placed on litmus paper neither makes it blue nor red. Each cc. of the solution of sodic hydrate used corresponds to 10 mgrm. of oxalic acid.

10. *Determination of the Sulphuric Acids* (§ 69).

100 cc. of urine are heated to boiling after the addition of 20 or 30 drops of hydrochloric acid, and a standard solution of chloride of barium, each cubic centimeter of which indicates 10 mgrm. of sulphuric acid, is added drop by drop until the neutral point has been reached (§ 69, A), or until a slight excess of barium is indicated by sulphate of potassium in a filtered specimen. If 12 cc. have been required up to this point, but no reaction with sulphate of potassium has taken place when 11 cc. have been used, the true amount lies between 11 and 12 cc. We immediately add 11 cc. of the chloride of barium solution to a new quantity, heat to boiling, and complete the estimation exactly according to § 69, C.

11. *Determination of the Sugar* (§ 70).

In this estimation the urine must be diluted so that it contains at most  $\frac{1}{2}$  per cent. of sugar. 10 cc. of the standard copper solution are then measured off, diluted with 40 cc. of water, heated to boiling, and the dilute urine added until all of the copper has been reduced, and a filtered specimen, after being rendered acid by hydrochloric acid, no longer gives the copper test with sulphuretted hydrogen. In most cases a proper dilution is attained by mixing 5 cc. of diabetic urine with 95 cc. of water. However, the dilution must depend on the greater or less quantity of sugar in the urine.

The volume of urine employed for the complete reduction contains exactly 50 mgrm. of diabetic sugar. If now we have diluted the urine, for example, to twenty times its volume before

testing, we must divide  $20 \times 5 = 100$  by the number of cubic centimeters used in order to obtain the percentage of sugar in the urine (§ 70, C). Knapp's method is equally accurate (§ 70, 2).

The estimation of sugar optically with the polariscope is more quickly accomplished (§ 70, 3).

Very satisfactory results are also obtained by the difference of the specific gravity before and after fermentation. (Manassein's method, § 70, 5.)

12. *Determination of the Albumen* (§ 75).

The process is carried out just as described in § 75.

13. *Determination of the Uric Acid* (§ 73).

200 cc. of urine are treated with 5 cc. of hydrochloric acid of 1.11 sp. gr., covered and left at rest from twenty-four to thirty-six hours in a cool place at a temperature of  $10^{\circ}$  or  $15^{\circ}$  C. (in most cases twenty-four hours are sufficient); the fluid is then drawn off with a siphon, and lastly the crystals are collected on a small dried and weighed filter. After washing (the drops which come away should not have an acid reaction) it is dried at  $100^{\circ}$  C. and weighed (§ 73).

14. *Determination of the Kreatinin.*

We proceed exactly according to § 74, C.

15. *Determination of the Calcium* (§ 76, I, C).

200 cc. of urine are treated with ammonia, the resulting precipitate dissolved in as little acetic acid as possible, and the calcium precipitated with oxalate of ammonium. When the fluid has become perfectly clear it is drawn off with a siphon, the calcic oxalate is collected on a filter, washed, ignited, and titrated with hydrochloric acid and sodic hydrate solution, as described in § 76, C. 1 cc. of saturated hydrochloric acid corresponds to 10 mgrm. of  $\text{CaO}$ , or 18.45 mgrm. of  $3\text{CaO}, \text{PO}_4$ .

16. *Determination of the Magnesium* (§ 76, II. 1).

a. The fluid obtained in 15 is united with the wash water, and the magnesium is precipitated by ammonia as ammonio-magnesian phosphate. After twelve hours the clear fluid is drawn off with a siphon, the precipitate collected on a filter, washed with water containing ammonia, ignited, and weighed (§ 76, II. 1). Or the phosphate of magnesium is dissolved in acetic acid, and the magnesium determined by titrating the phosphoric acid contained in the precipitate, as described in § 76, II. 2.



b. 200 cc. of urine are precipitated with ammonia, the earthy phosphates which separate are collected on a filter after a few hours, washed with water containing ammonia, dried and ignited just as we have described in § 76, II. 1, b. The quantity of phosphate of calcium obtained subtracted from the quantity of earthy phosphates found gives as a remainder the quantity of phosphate of magnesium ( $2\text{MgOPO}_3$ ) which was present. I prefer this second process to the one described under a.

17. *Determination of the Ammonia* (§ 77).

20 cc. of urine are mixed with milk of lime and placed in the apparatus described and figured in § 77, C, beside a measured volume of standard sulphuric acid, and the non-saturated portion of the acid, after forty-eight hours, is titrated back with sodic hydrate of known strength (§ 77, C).

18. *Determination of the Iron* (§ 72).

200 cc. of urine are evaporated to dryness, ignited according to § 60, until all of the carbon is consumed, dissolved in hydrochloric acid, the oxide of iron which is formed is reduced by boiling with sulphite of sodium, allowed to cool, diluted to 60 cc., and the iron present determined by a solution of permanganate of potassium, whose strength has been ascertained just before using it by a solution of oxalic acid or ferrocyanide of potassium (§ 72).

19. *Determination of the Potassium and Sodium.*

We proceed as in § 79.

20. *Determination of the Fat.*

According to § 82.

21. *Determination of the free Carbonic Acid.*

We proceed exactly as in § 80.

22. *Determination of the Iodine.*

After the method given in § 71.

23. *Determination of the Total Nitrogen contained in the Urine* (§ 81).

24. *Determination of the Indican* (§ 84).

25. *Determination of the Oxalic Acid in Solution* (§ 85).

26. *Determination of Biliary Acids* (§ 83).



## IV. PRACTICAL GUIDE FOR APPROXIMATE ESTIMATIONS.

## § 91.

Although we are able by means of the different volumetric methods to ascertain with certainty and rapidity the quantity of very many constituents of the urine, still cases occur in which the physician wishes to determine immediately whether a urine contains more or less of a certain constituent than has been the case at another time. But since it is not necessary to give a special guide for approximately estimating every constituent, the two methods employed by Beneke \* may serve as examples of others.

1. *Estimation of the Earthy Phosphates by the Method of Beneke.*

The earthy phosphates are known to be held in solution in the urine by the free acids, and separate when the urine becomes alkaline.

If, therefore, we saturate the free acid of the urine with any alkali, we obtain a precipitate if the urine contains earthy phosphates. According to the amount of the earthy phosphates in solution there will be either no cloudiness at all or only a very slight one, and sometimes a larger, sometimes a smaller precipitate will result. These differences are characteristic enough to enable us to draw an approximate conclusion as to the quantity present.

If we always use for such estimations a vessel of the same diameter, which at a certain mark contains exactly 15 or 20 cc., we can, as the large number of experiments performed by Beneke show, soon distinguish quite definitely different degrees of cloudiness or precipitation. If we first establish a scale for the different degrees of cloudiness which arise, and, secondly, determine by accurate analysis the actual quantity corresponding to each degree of the scale, we have all of the conditions which are requisite for the performance of such an analysis.

For estimating the earthy phosphates seven degrees of cloudiness are distinguished by Beneke, and the amount cor-

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\* Beneke, *Zur Physiologie und Pathologie des phosphorsauren und oxalsauren Kalks*, Göttingen, 1850.

responding to these was determined according to the method described in § 76.

Beneke marks :

1. With 0, a urine which, after being boiled in a test tube and treated with 5, 10, or 15 drops of a sodic hydrate solution (one part of sodic hydrate in twelve parts of water), showed no cloudiness, but remained as clear as before.

2. With  $\frac{1}{2}$ , a urine which when similarly treated showed a slight opacity.

3. With 1, a urine which, treated in the same way, gave a strong opacity, yet of such a kind that objects behind the glass, as, for example, the frames and borders of a window, could be distinguished through it.

4. With  $1\frac{1}{2}$ , a urine which, after the addition of sodic hydrate, gave so great a degree of cloudiness, yet still somewhat opalescent, that an object behind the glass could scarcely be distinguished.

5. With 2, a urine which becomes very turbid and loses its opalescence.

6. With  $2\frac{1}{2}$ , a urine which yields a considerable precipitate of earthy phosphates a few seconds after adding the sodic hydrate.

7. With 3, a urine which immediately gives a large precipitate.

8. With 3 to 4, finally, a urine which separated a very large quantity of earthy phosphates immediately after the addition of sodic hydrate.

It is easy to see that we may become so familiar with the different degrees of cloudiness by frequent repetition of this sort of test, that a specimen may readily be classified according to the scale. Cases occur, however, in which the appearances do not agree with any one of the given numbers; such may be designated with sufficient accuracy by saying  $\frac{1}{4}$ ,  $\frac{3}{4}$ ,  $1\frac{1}{4}$ ,  $1\frac{1}{2}$ , etc.

If the urine is alkaline any sediment of earthy phosphates which is present is equally divided, one portion of the urine is then boiled, and, according as the alkaline reaction is weak or strong, only a little or none of the solution of sodic hydrate is added. If the urine contains albumen, it is coagulated by boiling, filtered, and the filtrate then tested for phosphates.

Beneke has found by accurate analysis that the scale he gives corresponds to the following quantities in an ounce of urine :

Urine marked 0 contains about 0·100 or 0·150 grm. of earthy phosphates.

"	"	$\frac{1}{4}$	"	"	0·250	"	0·300	"	"	"
"	"	1	"	"	0·400	"	0·450	"	"	"
"	"	$1\frac{1}{4}$	"	"	0·550	"	0·600	"	"	"
"	"	2	"	"	0·700	"	0·750	"	"	"
"	"	$2\frac{1}{4}$	"	"	0·850	"	0·900	"	"	"
"	"	3	"	"	1·000	"	1·050	"	"	"
"	"	3 to 4	"	"	1·000	"	1·300	"	"	"

We can thus easily reckon approximately how much earthy phosphates are passed with the urine in twenty-four hours.

2. *Estimation of the Calcic Oxalate by Beneke's Method.* To estimate the quantity of calcic oxalate approximately, Beneke used a method similar to the one just described, which, in brief, is as follows: In testing for calcic oxalate it is necessary, on each occasion, to allow a portion of the urine under investigation to stand twenty-four hours in a test tube. If at the end of this time a sediment has formed in the lowest part of the glass, the clear fluid is poured off and one of the last drops examined under the microscope. This test must not be omitted, even if no distinct cloudiness is observed in the specimen. If we find a sediment of urates, the drop is warmed on the glass slide to dissolve the urates, and the calcium phosphate is removed by a drop of acetic acid, when the calcic oxalate will remain behind alone in most cases. By operating in this way, by always examining only one drop of the sediment on the slide, and by covering the drop with a thin covering glass, we will be able to decide as to the quantity of calcic oxalate present.

To get a better idea, Beneke has here, also, distinguished the different quantities with numbers:

Urine marked 0 contains no calcic oxalate.

"	"	$\frac{1}{4}$	"	very little calcic oxalate.		
"	"	1	"	little	"	"
"	"	$1\frac{1}{4}$	"	a moderate amount of calcic oxalate.		
"	"	2	"	considerable	"	"
"	"	$2\frac{1}{4}$	"	much	"	"
"	"	3 to 4	"	an exceedingly large quantity of calcic oxalate.		

Since it is quite apparent that each person must make such a scale for himself, I content myself with having brought forward these two methods of Beneke, similar to which others may be easily arranged for albumen, uric acid, sulphuric acid, etc. Such approximate estimates, however, can lay no claim to great accuracy.

## ANALYTICAL EXPERIMENTS.

## § 92.

**I. Table for Estimating the Total Solids from the Specific Gravity (§ 59, 3).**

SPECIFIC GRAVITY.	SOLIDS FOUND BY WEIGHING.	SOLIDS CALCULATED BY MULTIPLYING BY 0.233.
	PER THOUSAND.	PER THOUSAND.
1.0160	37.4	37.28
1.0260	62.0	60.58
1.0154	35.1	35.88
1.0261	60.2	60.81
1.0213	48.6	49.63
1.0230	56.4	53.59
1.0230	56.0	53.59
1.0225	49.3	52.42
1.0240	54.1	55.92
1.0257	60.4	59.88
1.0275	63.9	64.07
1.0275	64.2	64.07
1.0217	48.5	50.56
1.0223	52.15	51.96
1.0140	31.08	32.62
1.0236	56.64	54.98
1.0133	30.87	30.99
1.0134	31.06	31.22
1.0238	57.09	55.45
1.0250	60.47	58.25
1.0164	37.26	38.21
1.0135	33.35	31.45
1.0210	48.54	48.93
1.0137	32.55	31.92
1.0085	19.16	19.80
1.0110	24.96	25.63
1.0200	Average 46.59	46.52

From these determinations we find that by dividing the mean quantity of solid constituents found in 1,000 grm. of urine by the last three decimals of the mean sp. gr., we obtain the quotient 0·23295, for which we may conveniently put down the number 0·233, as Häser suggests. By multiplying with this quotient the three last decimals of the sp. gr. carried out to four places of decimals, we obtain the figures given in the third column, whose difference from those obtained by gravimetric analysis may be seen in the above table. If, however, the specific gravity has been determined only to three decimals, the second and third figures multiplied by 2·33 give, approximately, the amount of solid matters in 1,000 parts of urine.

## II. *Determination of the Chlorine (§ 66).*

The comparative analyses were carried out according to the following methods :

a. 5 cc. of urine were evaporated with nitre, the organic matters destroyed by ignition, and the chlorine determined by a solution of nitrate of silver.

b. 5 cc. of urine were heated with different quantities of permanganate of potassium solution (four grm. to the liter), and the chlorine in the filtrate titrated with nitrate of silver solution.

c. 5 cc. of urine were diluted with 10 cc. of water, and the chlorine directly titrated with a solution of nitrate of silver.

### *1st Series. Mixed urine of twenty-four hours.*

1. According to a there were found  $\left\{ \begin{array}{l} 7\cdot5 \text{ per thousand of NaCl.} \\ 7\cdot6 \quad \quad \quad \text{“} \quad \quad \text{“} \\ 7\cdot6 \quad \quad \quad \text{“} \quad \quad \text{“} \end{array} \right.$

2. According to b,

5 cc. of urine with 10 cc. of permanganate solution 8·8 per thousand of NaCl.

5 cc.    “    “    20 cc.    “    “    8·8    “    “

5 cc.    “    “    30 cc.    “    “    8·5    “    “

5 cc.    “    “    40 cc.    “    “    8·2    “    “

3. According to c there were found                      9·2 to 9·4 “    “

### *2d Series. The mixed twenty-four hours' urine.*

1. According to a there were found  $\left\{ \begin{array}{l} 6\cdot1 \text{ per thousand of NaCl.} \\ 6\cdot1 \quad \quad \quad \text{“} \quad \quad \text{“} \end{array} \right.$

2. According to b,

5 cc. of urine with 20 cc. of permanganate solution  $\left\{ \begin{array}{l} 6\cdot4 \text{ per thousand NaCl.} \\ 6\cdot45 \quad \quad \quad \text{“} \quad \quad \text{“} \end{array} \right.$

5 cc. of urine with 80 cc. of permanganate solution  $\left\{ \begin{array}{l} 6.2 \text{ per thousand NaCl.} \\ 6.8 \text{ " " " } \end{array} \right.$

(A slight excess of permanganate must be destroyed by a few drops of oxalic acid solution.)

8. According to c there were found 6.6 to 6.8 per thousand of NaCl.

### 3d Series. Concentrated morning urine.

1. According to a there were found  $\left\{ \begin{array}{l} 4.5 \text{ per thousand of NaCl.} \\ 4.6 \text{ " " " } \end{array} \right.$

2. According to b,

5 cc. of urine with 50 cc. of permanganate solution  $\left\{ \begin{array}{l} 4.9 \text{ per thousand of NaCl.} \\ 4.9 \text{ " " " } \end{array} \right.$

(A slight excess of permanganate must be decomposed by a few drops of oxalic acid solution.)

8. According to c there were found  $\left\{ \begin{array}{l} 5.8 \text{ per thousand of NaCl.} \\ 5.7 \text{ " " " } \\ 5.7 \text{ " " " } \end{array} \right.$

The procedure a, therefore, yields the most accurate results.

### III. Determination of the Phosphoric Acid. With oxide of uranium solution (§ 67).

The titration was performed according to the directions given above for every 50 cc. of urine; the gravimetric estimation, on the other hand, for every 100 cc., according to the ordinary method and with the observance of all requisite precautions. The ammonio-magnesian phosphate before ignition was moistened with a few drops of a concentrated solution of nitrate of ammonium, and thus the phosphate of magnesium obtained perfectly white. It gave the following results:

	Volumetric Analysis.	Gravimetric Analysis.
100 cc.	0.1802	$\left\{ \begin{array}{l} 0.1803 \\ 0.1299 \end{array} \right.$
100 cc.	0.2852	0.2342
100 cc.	0.1889	$\left\{ \begin{array}{l} 0.1883 \\ 0.1410? \end{array} \right.$
100 cc.	0.1812	$\left\{ \begin{array}{l} 0.1818 \\ 0.1824 \end{array} \right.$

### IV. Determination of the Sulphuric Acid (§ 69).

The sulphuric acid in each 100 cc. of urine was determined by weighing and by the volumetric method, and the following results obtained:

Gravimetric.	Volumetric.
0.129 grm. SO <sub>3</sub>	0.128 grm. SO <sub>3</sub>
0.182   "   "	0.177   "   "
0.274   "   "	0.270   "   "
0.189   "   "	0.187   "   "
0.235   "   "	0.238   "   "

### V. Determination of Sugar (§ 70).

1. 0.4 grm. of pure grape sugar was dissolved in 20 cc. of urine and diluted to 100 cc.; the urine consequently contained 2 per cent. of sugar. 12.3 cc. were required to reduce 10 cc. of the copper solution. There were found, therefore,

$$\frac{5 \times 5}{12.3} = 2.03 \text{ per cent.}$$

0.6 grm. of grape sugar was dissolved in 20 cc. of urine and diluted to 100 cc.; the urine, therefore, contained 3 per cent. of sugar. 8.4 cc. were required to reduce 10 cc. of the copper solution. There was found, therefore,

$$\frac{5 \times 5}{8.4} = 2.97 \text{ per cent.}$$

2 grm. of grape sugar were dissolved in 20 cc. of urine and diluted to 400 cc.; the urine then contained 10 per cent. of sugar. 10.5 cc. were required to reduce 10 cc. of the copper solution. There was found, therefore,

$$\frac{20 \times 5}{10.5} = 9.5 \text{ per cent.}$$

2. Comparative experiments with diabetic urine carried out by the methods of Fehling, Knapp, and optically with the Ventzke-Soleil apparatus, gave the following results:

a. According to Fehling's method	. . . .	3.59 per cent.
"          Knapp's          "	. . . .	3.68   "
By circumpolarization	. . . .	2.40   "
b. According to Fehling's method	. . . .	3.67   "
"          Knapp's          "	. . . .	3.47   "
By circumpolarization	. . . .	2.10   "

# VI. *Determination of the Kreatinin (§ 74).*

0.8938 gm. of kreatinin, the purity of which was proved by estimating the nitrogen, were dissolved in 2 or 3 cc. of water and diluted to 160 cc. with absolute alcohol. Each 50 cc. of this solution, in which 0.2793 gm. of kreatinin was dissolved, were measured off and precipitated by adding  $\frac{1}{2}$  cc. of an alcoholic solution of chloride of zinc of 1.195 sp. gr. After standing forty-eight hours in a cool place the resulting precipitate was carefully collected on a weighed filter, and dried at 100° C., the filtrate first obtained always being used for collecting the precipitate on the filter. The washing with absolute alcohol was only commenced when the mother liquor had completely run off. When dried at 100° the following results were obtained:

1. 0.2793 gm. of kreatinin gave 0.4438 gm. of kreatinin chloride of zinc corresponding to 99.2 per cent.
2. 0.2793 gm. of kreatinin gave 0.4429 gm. of kreatinin chloride of zinc corresponding to 99.0 per cent.
3. 0.2793 gm. of kreatinin gave 0.4439 gm. of kreatinin chloride of zinc corresponding to 99.2 per cent.

As an additional measure an estimation of the nitrogen was made with the kreatinin chloride of zinc obtained from the alcoholic solution: 0.3453 gm. dried at 100° C. gave 0.0798 gm. of N; corresponding to 23.1 per cent of N, while the calculation required 23.21 per cent. 100 parts of kreatinin chloride of zinc dried at 100° C. correspond, therefore, to 62.44 per cent. of kreatinin.

From the above calculations it appears, therefore, that the estimation of kreatinin with chloride of zinc nearly equals in accuracy the estimation of potassium with platonic chloride.

# VII. *Determination of the Albumen (§ 75).*

Double analyses by weight were very carefully made with clear filtered urine containing a solution of albumen.

1. a. 100 cc. gave 1.130 gm. of albumen dried at 100° C.  
    b. 100 cc.   "   1.107   "                   "                   "
2. a. 100 cc.   "   0.624   "                   "                   "  
    b. 100 cc.   "   0.616   "                   "                   "
3. a. 100 cc.   "   0.600   "                   "                   "  
    b. 100 cc.   "   0.588   "                   "                   "

# VIII. *Determination of the Calcium (§ 76).*

0.222 gm. of calcic phosphate were converted into carbonate



according to § 76, 1, and then dissolved in 20 cc. of hydrochloric acid, 1 cc. of which corresponded to 10 mgrm. of CaO. 10.2 cc. of sodic hydrate solution of corresponding strength were required for titrating back; consequently  $20 - 10.2 = 9.8$  cc. of hydrochloric acid were saturated by the lime.

The 0.222 gm. of calcic phosphate contained, therefore, 0.098 gm. = 44.14 per cent. of CaO. The gravimetric estimation gave 44.20 per cent. of CaO.

Each 100 cc. of the same urine treated by this method gave a percentage of 0.0420 and 0.423 of lime.

#### IX. *Determination of the Ammonia* (§ 77).

The sulphuric acid employed in these experiments contained 0.5304 gm. of  $\text{SO}_4$  in 10 cc., corresponding to 0.22542 gm. of  $\text{NH}_3$ . 22.1 cc. of solution of sodic hydrate were required to saturate 10 cc.; 1 cc. of sodic hydrate solution, therefore, corresponded to  $\frac{0.22542}{22.1} = 0.0102$  gm.  $\text{NH}_3$ .

1. 10 cc. of urine were directly treated with milk of lime. After forty-eight hours the  $\text{NH}_3$  evolved corresponded to 0.8 cc. of the sodic hydrate solution. Consequently the urine contained 0.081 per cent. of  $\text{NH}_3$ .

2. 40 cc. of the same urine were freed from the coloring and extractive matters by 40 cc. of the mixture of the acetate and basic acetate of lead solutions. 20 cc. of the clear filtrate, corresponding to 10 cc. of urine, after forty-eight hours had evolved the same quantity of  $\text{NH}_3$ ; 0.8 cc. of the sodic hydrate solution was saturated.

After another forty-eight hours the two specimens had evolved no more  $\text{NH}_3$ .

3. To 10 cc. of the same urine 0.2343 gm. of chloride of ammonium dried at  $100^\circ \text{C}$ . were added. At the end of the experiment 14.1 cc. of the sodic hydrate solution were required to saturate the 10 cc. of sulphuric acid. The  $\text{NH}_3$  evolved corresponded, therefore, to  $22.1 - 14.1 = 8$  cc. of sodic hydrate solution.

The 10 cc. of urine alone corresponded to 0.8 cc. of sodic hydrate solution; there remains then  $8.0 - 0.8 = 7.2$  cc. of sodic hydrate solution for the chloride of ammonium added. 7.2 cc. of sodic hydrate correspond to  $(7.2 \times 0.0102) = 0.07344$  gm.  $\text{NH}_3$ , and this  $(17.5346 = 0.07344 : x) = 0.2309$  gm. of chloride of

ammonium. Thus 0.2309 gm. were found again for the 0.2343 gm. added.

4. 10 cc. of another specimen of urine were treated directly with milk of lime. The  $\text{NH}_3$  evolved corresponded to 1.25 cc. of sodic hydrate. So that the urine contained 0.1275 per cent. of  $\text{NH}_3$ .

After another forty-eight hours no more  $\text{NH}_3$  was evolved.

5. 10 cc. of the same urine were treated with 0.1744 gm. of chloride of ammonium. After the end of the experiment 15.4 cc. of sodic hydrate were required to saturate the 10 cc. of  $\text{SO}_2$ . The  $\text{NH}_3$  evolved, therefore, corresponded to  $22.1 - 15.4 = 6.7$  cc. of sodic hydrate. The 10 cc. of urine alone corresponded to 1.25 cc., and thus there remained  $6.7 - 1.25 = 5.45$  cc. of sodic hydrate for the chloride of ammonium added. 5.45 cc. correspond to  $(5.45 \times 0.0102) = 0.05559$  gm. of  $\text{NH}_3$ , and this to 0.1747 gm. of chloride of ammonium. Instead of the 0.1744 gm. added, then 0.1747 gm. of chloride of ammonium were found.



# PART SECOND.

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THE SEMIOLOGY OF HUMAN URINE;

OR,

THE ESTIMATION AND SIGNIFICANCE OF THE CHANGES OF  
THIS FLUID :

TOGETHER WITH A

GUIDE TO THE EXAMINATION OF URINARY CALCULI AND  
OTHER URINARY CONCRETIONS,

WITH SPECIAL REFERENCE TO THE PURPOSES OF THE PRACTISING PHYSICIAN.

BY

JULIUS VOGEL.



## INTRODUCTION.

THE study and analysis of the urine has been regarded from the earliest times as of great assistance in recognizing and forming an opinion concerning diseased conditions. Nevertheless, before the chemical and microscopic methods of examination were perfected, the real value of this branch of science was slight, and the *inspection of the urine*, often misused by charlatans to deceive an ignorant public, consequently for a long time fell into discredit both with scientific physicians and the educated portion of the public.\* With the improvement of organic chemistry and the general use of the microscope, *uroscopy* first assumed a scientific character, and no one now doubts that it is entitled to form an important and essential part of semiology and diagnosis. Many important diseases are distinctly recognized and accurately determined only by an examination of the urine : thus the different forms of diabetes, most kinds of nephritis, etc., many conditions dangerous to the health, can only be warded off by observing the changes of the urine, such as the risk of the formation of a calculus, etc.

The aid which an examination of the urine renders the physician in reference to diagnosis, prognosis, and treatment may be of two kinds. An examination of the urine enables us to draw conclusions :

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\*Unfortunately this method of inspecting urine practised by charlatans threatens to crop out again at the present time. The author has had frequent opportunity to convince himself of this ; indeed, it is not merely uneducated persons belonging to the lowest classes of society who allow themselves to be deceived by such "marvellous doctors," but also people who belong to the higher and especially "educated" masses. Under such circumstances it doubly becomes the duty of physicians to point out to the public what aid a scientific study of the urine can furnish in the diagnosis, prognosis, and treatment of different diseases.

1. As to the *general* conditions of the economy, the relations of metamorphosis, character of the blood, the digestion, etc.

2. As to certain *local* diseases of organs belonging to the uro-poëtic system.

In the following pages we shall as far as possible consider both of these points equally.

Moreover, the examination of the urine may sometimes give information concerning special facts and processes which possess a certain importance for the physician. Thus we are frequently able from the mere inspection of the urine to determine whether a patient has a fever or not. From the odor or the color of the urine we know that certain articles of food or medicine have been taken, for example asparagus, oil of turpentine, rhubarb, etc. From the appearance of spermatozoa in the urine we know that a masturbation or coitus has taken place; from the presence of albumen in the urine we can conclude under certain circumstances that the patient is dropsical; or when the urine contains biliary coloring matters that jaundice exists, etc. The crafty physician makes use of such indications to gain the confidence of his patient in his knowledge or to retain it; but the scientific physician will avail himself of them cautiously and without ostentation, since any misuse of such means stamps him as a charlatan in the eyes of his colleagues and of the public.

In many cases an examination of the urine is of great importance to therapeutists, since it proves whether certain substances which a patient has used as medicine are eliminated again with the urine or not. In the latter case the physician is cautioned that by a continued use of many medicines he may readily produce a so-called cumulative action in the system which is dangerous, as is the case with nitre, digitalis, strychnia, etc. In the former case, on the other hand, he will be prompted to continue the agent, or even to increase the dose, when it is desirable to keep the system to a certain degree saturated with it for a long time, so that it may have its complete effect slowly and gradually, as with iodide of potassium, alkaline carbonates, and the like. The importance of examining the urine for such purely therapeutical purposes has not been hitherto sufficiently valued in practice. Its application, however, will surely increase in proportion as the analytical processes necessary to

carry it out, now difficult and incomplete, are further perfected, simplified, and rendered easy for the physician—a problem whose solution the author would most earnestly recommend to those chemists who are interested in the subject.

If the science of urinary examination in reference to the above point has been hitherto neglected, there are, on the other hand, other points in regard to which its value has been overestimated. Many special facts will be mentioned later in this connection. One erroneous opinion, however, which is based on an imperfect knowledge of the nutritive changes in disease and upon an ontological way of regarding single forms of disease not yet discarded by all pathologists, deserves mention and a refutation, because it and the conclusions drawn from it have a very great range and are widely spread, and have even appeared anew in recent works on these subjects. It is, the opinion that the different forms of disease are characterized by a definite condition of the urine which corresponds to each. This statement is only true for a very few diseases, in which a certain condition has received its name from a characteristic condition of the urine. It is natural that the urine in albuminuria should contain albumen, in hæmaturia blood, in glycosuria sugar, in oxaluria oxalic acid, etc.; if this were not the case, we should not be justified in giving this name to the disease. In other forms of disease we only very rarely find any specially characteristic condition of the urine; and when recently it has been several times asserted that the urine, for example, in typhoid fever, pneumonia, etc., has possessed a certain composition or qualities, such observations, as a rule, rest on insufficient data or the investigations have been made in certain stages of these diseases only.

Examinations of the urine in the above diseases in which they have been made in great number and in all stages of the disease show, as will be proved later, that the condition of the urine in all acute diseases changes with the progress of the disease, with a certain degree of regularity. And that this change in the condition of the urine ordinarily depends less on the special nature of the sickness, especially its local phenomena, than upon certain general conditions of the body, such as the intensity of the fever, the state of the appetite and digestion, that is, upon the greater or less amount of food taken. This is also true of



chronic diseases in which acute exacerbations occur, as is often the case. For example, the wide-spread idea that the amount of urea in the urine in Bright's disease is diminished is untrue to this extent: that in febrile forms of this disease, just as is the rule in all fevers, an increase of the urea is observed.

Therefore, it appeared better to consider in the following pages only the *general* semiology of the urine, since the *special* semiology of this fluid, that is, the description of the composition of the urine in individual diseases, is best left to the consideration of each disease, that is, to special pathology.

To render more easy the general study and the solving of certain questions, the following pages have been divided into two principal divisions and several subdivisions.

The first division discusses the qualitative changes of the urine including the sediment. It contains four subdivisions:

- I. Changes in color, appearance, and odor of the urine.
- II. The chemical reaction of the urine and its significance.
- III. The occurrence of unusual or abnormal constituents in the urine.
- IV. Urinary sediments.

The second division comprises the quantitative changes of the urine: the increase and diminution of the normal constituents.

It is subdivided into two large groups:

I. Quantitative changes of the urine which can be determined without chemical analysis, and which, on account of their easy detection, are especially important to the physician.

II. Quantitative changes which require a quantitative chemical analysis for their demonstration.

A guide to the examination of urinary calculi and other urinary concretions is added as an appendix.

Those who desire to study more minutely the changes of the urine which occur in disease, especially in regard to their diagnostic significance and the therapeutic indications which they give the physician, are referred to my work on the *diseases of the kidneys* (including the changes in the urine which occur in general diseases) in the *Handbuch der speciellen Pathologie und Ther-*

*apie*, Band 6, edited by Virchow, and published by F. Enke in Erlangen.

Since the author had in view especially the needs of the physician, it appeared best, owing to the necessity of as condensed a statement as possible, to communicate the results of many labors on human urine during the last few years only so far as they were of interest not merely to chemists and physiologists but to the physician. But to satisfy those who wish to inform themselves somewhat more in detail than the space here permits on many points, especially as to questions which are still *sub judice*, the literature which contained further information in regard to them was referred to.

Moreover, to avoid repetition, all which has already been mentioned in the first part has been omitted, and we have only referred to the sections concerned, or to the numbers of the pages.



## DIVISION FIRST.

### QUALITATIVE CHANGES OF THE URINE, INCLUDING URINARY SEDIMENTS.

#### I. CHANGES IN THE COLOR, APPEARANCE, AND ODOR OF THE URINE.

THE changes of the urine which belong under this head are naturally the most easily detected; but of themselves alone they rarely lead to positive diagnostic and semiotic conclusions. Usually they only serve as hints and guides to a further investigation of the urine by other means. Therefore, the *mere inspection of the urine* without using other additional methods of investigation is of relatively little value to the physician.

#### § 93. COLOR OF THE URINE.

The color of the urine is due to the coloring matters, whose nature and origin, in spite of numerous investigations, has thus far not been completely explained. For what is known on this point see § 10. We shall only speak of those points here which have an importance to the medical practitioner. (Compare § 122)

The color of the urine is an important sign which sometimes gives the practitioner valuable indications for judging of the condition of a disease; but still more frequently it may serve to give him a general idea of it, and to point out to him the direction for his further investigations.

As practitioners we must distinguish between *normal* and *abnormal* color of the urine.

1. The *normal color* of the urine is yellow, with a greater or less admixture with red. It varies from almost colorless (like water), through yellow, to red and reddish brown.

These different shades of color of normal urine may be classified in the following principal groups :

*Pale*—colorless to straw yellow.\*

*Normal*—gold to amber yellow.†

*High color*—reddish yellow to red.‡

*Dark*—with a brownish tint, dark beer-color to blackish.§

A *pale urine* contains little coloring matter, little urea, and, as a rule, also only little solid constituents (except diabetes mellitus). It is seldom very acid, frequently neutral or alkaline. It is observed in persons in perfect health after copious drinking (*urina potus*), in many who are suffering from chronic diseases (anæmia, chlorosis, diabetes), as well as frequently in convalescents from severe acute diseases. The existence of a pale urine is *an almost absolute indication to the physician that the patient in question does not suffer from a severe acute febrile disease*, and a urine which continues to be very pale for a long time always indicates a certain degree of anæmia (oligocythæmia).

*Normally colored* urine only warrants the negative conclusion, that no disease exists which from its nature is characterized by a very pale or very high-colored urine.

*High-colored* urine is generally concentrated, abounds in solid constituents (has, therefore, a high specific gravity), is rich in urea, and usually very acid. It occurs in cases in which the secretion of water by the kidneys is diminished, while the secretion of the other constituents of the urine is normal or even increased. It, therefore, occurs in perfectly healthy persons after eating hearty meals (*urina chyli*), or when they have perspired freely and drunk little, as after vigorous exercise. It occurs in almost all febrile diseases, and becomes, therefore, an important sign to the physician. In hectic fevers especially it is often a surer indication than the pulse and the temperature in deciding as to the intensity of a febrile increase of metamorphosis.

*Dark* urine, as a rule, indicates that an abnormal pigment is mixed with the urine, the determination and significance of which requires a more careful investigation.

Occasionally it is desirable to determine the color of a urine

\* Plate IV., fig. 1 and 2.

† Plate IV., fig. 2 to 4.

‡ Plate IV., fig. 5 and 6.

§ Plate IV., fig. 7 to 9.

more accurately than according to the above general categories. We then proceed according to § 61, and make use of the considerations mentioned in § 122 for drawing the conclusions therefrom.

Heller has given still another method for approximately determining the quantity of the ordinary urinary coloring matter named by him urophaëin.\* A little concentrated English sulphuric acid is poured into a beaker and about double its quantity of the urine to be tested is added. If the mixture is quickly stirred it becomes colored more or less dark brown or tarry black. From the intensity of the color we decide as to the amount of urophaëin present. Ziegler states that the most intense color is produced by this test in cases of chronic degeneration of the liver, especially cirrhosis of the liver, and he uses this urophaëin test as an aid in the diagnosis of this disease.

In many cases the color of the urine depends on different pigments which are present at the same time—soluble pigments which are dissolved in the urine, and insoluble ones which adhere to the sediments. It is, therefore, well to filter the urine in order to be better able to decide as to the part which the different pigments play in coloring the urine.

2. *Abnormal color* of the urine results from the presence of unusual coloring matters.

These unusual urinary pigments may be divided into two groups :

a. *Essential* abnormal colors of the urine, which are formed within the organism as the result of certain pathological processes, and, therefore, have an important significance for the practitioner.

b. *Accidental* abnormal colors, which get into the body from without, in the food, drink, or medicine, and are eliminated again with the urine, merely passing through the economy.

The most important abnormal colors of the urine are :

a. *The Essential*, caused

1. By *Blood Pigments*. These form very different shades according as the blood red is dissolved, in combination with the

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\* Compare Ziegler, *Die Uroscopie am Krankenbette*, Erlangen, Ferd. Enke, 1861, S. 24, *et seq.*

blood corpuscles, decomposed, unchanged, or present in the urine in greater or less quantity. The shades of color which are thus produced may vary from blood red (bright garnet red) to brown, brownish black, or even to an inky black. For the detection and the significance of this blood coloring matter in the urine, see § 99 and § 100, and the cases 11, 12, and 13 in § 134.

2. By *Biliary Pigments*. The color of this urine is yellowish green or brownish green. For the details see § 102.

3. By *Indican* (uroxanthin) and its products of decomposition, *uroglauclin* and *urrrhodin*. See § 10, page 67, *et seq.*\*

Uroxanthin rarely has any appreciable influence on the color of the urine; it is only in those cases in which, with a deficiency of urophaëin (urobilin), a large amount of uroxanthin is present, that the urine assumes a lemon-yellow color (in cholera and affections of the spine). To demonstrate the presence of uroxanthin, however, a chemical process is always necessary, as has been described already on page 71, C.

According to Baumstark,† *indican* belongs with hippuric acid, tyrosin, and the biliary acids in the chemical series of so-called "aromatic compounds," and is probably formed in the liver especially.

According to Jaffé's observations the small quantity of *indican* normally present in the urine is increased by a meat diet; it is diminished to a mere trace by a diet containing little nitrogen; according to Jaffé and Hoppe-Seyler, it is considerably increased in carcinoma of the liver, and also in cholera, according to Jaffé and Wyss.

According to Jaffé, diseases which bring about an obstruction of the small intestine (strangulated hernia, incarceration, etc.) very considerably increase the secretion of *indican* with the urine (ten or fifteen times the normal amount); obstruction of the large intestine increases it less, as experiments on dogs proved. In purulent peritonitis also, probably on account of the diminished motion of the small intestines, the *indican* is in-

\* Heller, in his *Archiv für Chemie und Microscopie*, 1852, S. 121, *et seq.* M. Jaffé (*Pflüger's Archiv*, iii., p. 448, *et seq.*). Ibid., Ueber den Ursprung des *Indicans* im Harn, *Centralbl. für d. medic. Wissenschaften*, 1872, p. 2. Ibid., Ueber die Ausscheidung des *Indicans* unter physiolog. u. patholog. Verhältnissen, *ibid.*, p. 481, *et seq.*, 497, *et seq.*

† *Berliner klin. Wochenschr.*, 1873, Nr. 4.

creased. Also in certain diarrhoeas (cholera and cholera morbus), but not in catarrh of the large intestine, accompanied by discharges at the same time from the large intestine only. Fever appears to have no essential influence on the amount of indican in the urine.

J. Rosenstern\* found the quantity of indican in the urine essentially increased in Addison's disease.

According to Heller† and his scholars, the amount of indican which can be detected in the urine is, in some degree, a measure of the amount of excitation of the nervous system, especially of the spinal cord (?). It is said to be increased in *urina spastica*, after too frequent coitus, onanism, etc., also in every irritation of the urinary organs, every acute and chronic disease of the kidney (nephritis, Bright's disease, perinephritis, etc.), and in many general diseases also, as typhoid fever, intermittent fever, cholera, and uræmia.

According to observations which R. Lawson (compare § 122) made in Jamaica, the urine of the inhabitants of the tropics is usually rich in indican, even under normal circumstances.

Uroglauclin and urrhodin, products of the decomposition of uroxanthin,‡ occur only rarely in the urine, when it has undergone decomposition in the bladder, with the production of a large amount of carbonate of ammonium (in cystitis and Bright's disease). It may then, however, give rise to very striking colors of the urine (green, blue, and violet.) Uroglauclin has a blue color, urrhodin a red color, and from a combination of these two with each other, and with the ordinary yellow urinary coloring matters many various shades of color may be produced.

Thus the urine may become green (greenish to beautiful grass green) when blue uroglauclin occurs in a yellow urine. It appears blue when the normal (yellow) coloring matter is wanting and uroglauclin predominates; violet, when uroglauclin and urrhodin are present together; reddish, when the latter predominates.

Uroglauclin and urrhodin usually form sediments, and, therefore, we must filter such a urine. Moreover, urrhodin dissolves

\* Virchow's Archiv, 1872, lvi., p. 27, *et seq.*

† Ziegler, loc. cit., p. 28.

‡ S. Kletzinsky in Heller's Archiv, 1853, p. 414, and Scherer in Ann. der Chemie und Pharmacie, Band 90, Heft 1, p. 120.



in ether with a beautiful carmine red color, uroglauclin dissolves in boiling alcohol with a beautiful blue color.

4. By *uroërythrin*, which sometimes, when dissolved in the urine, gives it a red color, sometimes when precipitated with sediments of uric acid and urates gives them a brick-red or rose-red color. Compare page 73.\*

The urine presents a very peculiar appearance in the majority of persons who suffer from melanotic cancer. Of the normal color when passed, it gradually becomes brown or even black when exposed to the air. This dark color appears still more quickly when oxidizing substances have been added, as nitric or chromic acid. This proceeds from a peculiar substance characteristic of melanotic cancer—*melanogen*. This peculiarity of the urine may be rendered serviceable for the diagnosis of melanotic cancer which is concealed in the internal organs, as, for example, in the liver.†

b. *Accidental*. Various coloring matters which enter the body as constituents of food, drink, and medicines may be eliminated again with the urine and color it. We have very numerous investigations on this point,‡ which, however, are less important to the physician than to the physiologist and chemist.

There are two coloring matters which we may speak of here which are also of interest to the physician, since they form constituents of medicines frequently used, and which often pass into the urine and may resemble urine colored by biliary coloring matter or more especially by blood. These pigments are *rhubarb* and *senna*. Each may color the urine brownish or even a deep blood red. Both can be readily distinguished from the color due to blood by chemical means, however. Urine which is colored by them on the addition of mineral acids becomes brighter, and light yellow, while urine containing blood is not made clearer by the acids, but in fact becomes rather darker.

After taking *santonin*, also, the urine receives a color similar to that produced by biliary matters (saffron yellow or greenish). It may be recognized from the fact that on the addition of an

\* Heller in his *Archiv*, 1853, p. 891, *et seq.*

† For details see Eiselt, *Prager Vierteljahreschr.*, 1858, S. 190, *et seq.*, u. 1862, S. 26, *et seq.* Bolze, *ibid.*, 1860, S. 140, *et seq.* Pribram, *ibid.*, 1865, S. 16, *et seq.*

‡ Compare the investigations of Kletzinsky in Heller's *Archiv f. Chemie und Mikr.*, 1852, p. 184, 211, 338.

alkali the yellow or greenish color, according to the amount of santonin present, becomes cherry red or purplish red.\*

After the use of carbolic acid or tar the urine at times assumes a blackish color. (Compare page 74.)

#### § 94. ODOR OF THE URINE.

The odor of the urine has no great importance for the physician. Many substances which give the urine a peculiar odor enter the economy from without, like the accidental coloring matters described in the previous section, and are separated again with the urine. Their presence may be serviceable to the physician as an indication that patients have taken certain articles of food or medicine. In this way the urine acquires a peculiar odor after asparagus has been eaten, a peculiar one (like violets) when oil of turpentine has been taken, or when it has simply been inhaled in large quantity. We may discover the odors of saffron, cubebs, etc., in the urine.

It has been asserted by French pathologists (De Beauvais and others) that the peculiar odors of asparagus, oil of turpentine, etc., do not appear in the urine in organic diseases of the kidney. However valuable this means of diagnosis might have been in cases of albuminuria in which the other symptoms left it doubtful whether a merely functional disturbance or an organic lesion of the kidney existed, I would, after some experiments of my own, advise that it be accepted with caution. I have found twice, for example, that the urine had the characteristic odor of asparagus and oil of turpentine in cases of albuminuria, when later the autopsy showed at least a partial organic disease of the parenchyma of the kidney.

But normal urine has a specific odor which Heller referred to the coloring matter of the urine (urophaëin), but which probably depends on various odorous matters, since Städeler succeeded by distilling the urine in obtaining several volatile acids from it (phenylic, taurylic, damaluric, and damolic acids). (Compare § 9.) A preponderance of one or the other of these would probably modify the odor of the urine.

The sense of smell is peculiarly affected by a urine which

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\* Walter G. Smith, Dublin Quart. Journ., c., p. 262, *et seq.*

contains much carbonate of ammonium, and the "urinous odor" of patients comes chiefly from this source.

### § 95. TRANSPARENCY OF THE URINE.

The urine is either clear or cloudy. Slight turbidities form a so-called cloud (*nubecula*), larger ones after standing a long time deposit as a precipitate, and form a sediment. All turbidities of the urine consist of solid particles which are not dissolved but are only suspended in it. They are either already contained in the fresh urine, or form in it a longer or shorter time after it is passed from the bladder.

A normal specimen of urine is always clear or at most has only a very slight degree of cloudiness. Distinct turbidity of the urine always allows us to conclude that there is some abnormal condition, and must, therefore, arouse the attention of the physician. But the significance of the turbidity only becomes clear, when we have ascertained its nature. (For further details, see Division IV. under Urinary Sediments.)

## II. CHEMICAL REACTION OF THE URINE.

### § 96.

Normal urine almost always has an acid reaction; that is, it colors blue litmus paper red. Sometimes, however, its reaction is neutral or even alkaline; in the latter case it renders red litmus paper blue.

It is most convenient in testing the reaction of urine to use a blue litmus paper, which has a very slight red tint. This serves equally well for detecting an acid as well as an alkaline reaction, since it is rendered more red by acid and deep blue by alkaline urine. It is, moreover, very sensitive. It is prepared by allowing an aqueous tincture of litmus to stand until it becomes slightly acid, and its intense blue color has assumed a reddish tint. Ordinary smooth writing paper is dipped in this tincture and dried in the shade.

Sometimes urine is met with which has both an acid and an alkaline reaction; that is, at the same time it slightly reddens blue litmus paper and blues slightly reddened paper. (Amphi-

genous reaction of Heller, or better, amphoterous reaction of Bamberger.)

This paradoxical phenomenon is probably to be explained as follows: When acid phosphate of sodium is neutralized by ammonia, a compound results (ammonio-sodic phosphate) which has the property of giving off ammonia when it is warmed and the pressure on it is diminished, while acid phosphate of sodium remains. If, now, ammonia is developed by the decomposition of urea in a urine naturally acid from the presence of acid phosphate of sodium, it may be unequally distributed in the fluid and render certain portions alkaline, or it may form an ammoniacal atmosphere above the fluid by which red litmus paper is made blue, while other portions of the same urine still contain acid phosphate of sodium, and, therefore, redden blue litmus paper. In the same manner we often observe that a specimen of urine which is commencing to evolve ammonia, but which still has a slightly acid reaction, has on its surface a pellicle of crystalline ammonio-magnesian phosphate, which according to its chemical properties cannot exist in an acid fluid.\*

The chemical reaction of the urine gives the physician several useful indications, and is, moreover, a test very easy to perform. It is, therefore, a valuable sign in semiology; and in order to render its importance clear we must study this subject further.

Normal urine has an acid reaction. It is not yet positively known on what acid this reaction of the urine depends. It is probable that it depends only in the rarest cases on the presence of a free acid (compare page 6 and § 11), but, as a rule, rather on the acid salts; indeed chiefly on the acid phosphate of sodium, and, perhaps, at the same time in many cases, on acid urates, hippurates, lactates, etc.

H. Baysson,† however, believes that the acid reaction of the urine does not depend on acid phosphates of the alkalies, but upon uric, carbonic, and hippuric acids, since uric and hippuric

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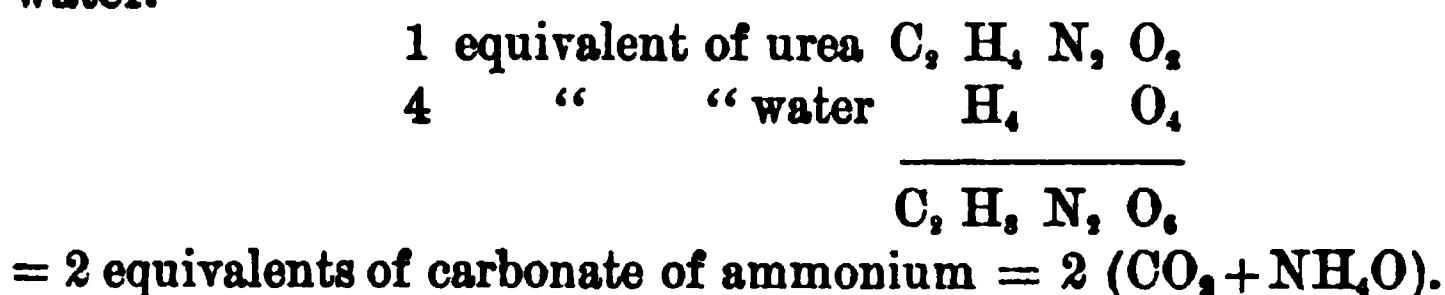
\* See further concerning the so-called amphoterous reaction: W. Heintz, *Journ. f. prakt. Chemie*, 1872, vi., p. 274, *et seq.*

† Etude sur les causes de la réaction acide de l'urine normale chez l'homme et de sa variation, *Journ. de l'anat. et physiol.*, par. Ch. Robin, 1872, t. viii., p. 383, *et seq.*

acids are not capable of decomposing neutral phosphate of sodium at ordinary temperatures.

There are, however, two essentially different ways in which the acid reaction of the urine may be lost or even changed to the alkaline.

1. Carbonate of ammonium may be formed in the urine after it is secreted ; the urine then becomes neutral if the quantity of carbonate of ammonium is small, alkaline when it is greater. This development of carbonate of ammonium is caused by a decomposition of urea, which under certain circumstances becomes converted into carbonate of ammonium by absorbing water.



This conversion of urea into carbonate of ammonium is caused by the presence of a ferment.

It was formerly the opinion that the mucus of the urinary passages constituted this ferment. Recent investigations, however, make it probable that it consists of microscopic germs, which decompose the urea by their development in the same way that yeast decomposes sugar in the alcoholic fermentation. Since the spores of this ferment are contained everywhere in the air on account of their extreme minuteness, they can very readily get into the urine. (Compare pages 7, 9, and 188.)

Under favorable conditions the urine may become alkaline while still within the urinary passages ; it is then alkaline when passed.

The urine thus becoming ammoniacal within the urinary passages has a very great practical importance, because it may be followed by very bad results : irritation of the mucous membrane of the urinary passages, blenorrhœa and even gangrene, formation of urinary concretions and ammonæmia. It is, therefore, very important to the physician to prevent it as much as possible and to remove its cause. Various recent observations have shown that these spores may enter the bladder on a catheter which is not perfectly clean, and to which the above-mentioned ferment may adhere. In the bladder they develop

further and cause the decomposition of urea there.\* The practical rule follows, therefore, that *every catheter must be most carefully cleaned before being used.*

Again, the alkalinity may appear only after the urine has been passed; it then has an acid reaction immediately after being passed and becomes alkaline only after a time. Almost every specimen of urine becomes alkaline in a longer or shorter time, but in normal urine this alkalinity occurs very late, at any rate not before twenty-four hours have elapsed. When, therefore, urine is evacuated in an alkaline state, or if it is acid when passed and becomes alkaline within twenty-four hours afterward, we may conclude that there are circumstances present which favor decomposition of the urea, and the physician is justified in drawing diagnostic conclusions from this circumstance.

But one circumstance is to be taken into consideration which, if it is overlooked, may lead to error. When urine which has already become alkaline is added to normal urine, the latter undergoes the ammoniacal fermentation much quicker than it otherwise would. This is the case when the urine is kept in a vessel which contains any remains of ammoniacal urine. When the physician, therefore, would draw conclusions from the fact of urine having become rapidly alkaline, say within twenty-four hours, he must be certain that it was kept in a perfectly clean vessel; he must, therefore, see that the chamber vessels and urine glasses of the patient are not merely emptied, but are also washed out, so that every trace of the ferment is removed.

Urine which has been rendered alkaline by carbonate of ammonium colors red litmus paper blue, but after *the paper has become dry* and the carbonate of ammonium has volatilized, while the acid salts of the urine remain behind, *the blue litmus paper becomes red again.* Moreover, a glass rod moistened with hydrochloric acid and held over such a urine develops a cloud of chloride of ammonium. This fact is important, because it serves to distinguish the alkalinity of the urine caused by carbonate of ammonium from that resulting from other causes.

V. Feltz and E. Ritter, professors at the academy of medicine in Nancy,† have arrived at the following results from their in-

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\* S. Fischer, Berliner klin. Wochenschr., 1864, 2. Teuffel, ibid. 16.

† Etude expérimentale sur l'alcalinité des urines et sur l'ammoniémie, im Journ. de l'anat. et physiol., par Ch. Robin, 1874, Nr. 8, p. 811, *et seq.*

vestigations: Unclean vessels are often the cause of urine becoming quickly ammoniacal, as in typhoid-fever patients in summer. The urine of women, which contains mucus from the vagina (in fluor albus) or menstrual blood, readily becomes alkaline. The ammoniacal fermentation is caused by a ferment, which may be readily obtained artificially on a filter through which ammoniacal urine has been passed. If this ferment is artificially added to normal urine, it has the power of setting up ammoniacal fermentation in it. However, all urines are not rendered ammoniacal with equal readiness by the addition of the ferment. By prolonged retention in the bladder alone (in animals whose urethræ were artificially closed) the urine is not rendered ammoniacal. The mere passing of a catheter impregnated with the ferment does not always certainly render the urine in the bladder ammoniacal.

2. There is still another cause essentially different from the one just described which may render the urine neutral or alkaline. This cause *lies in the condition of the blood*. Under ordinary circumstances *acid urine* is secreted from the *alkaline blood*. The kidneys or their secreting cells must, therefore, have the power of separating acid salts from the alkaline blood, or of forming them and passing them on into the urine.\* But when the blood is excessively alkaline, as a rule, acid urine is no longer separated from it, but neutral or alkaline. Thus the urine becomes alkaline when a large quantity of caustic alkalis or of carbonates of the alkalies are taken into the system, and it continues so until the excess is separated from the blood. Caustic soda, lime, potash, and magnesia, and their carbonates,

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\* [Dr. Richard Maly (Berichte der deutschen chemischen Gesellschaft, 1876, page 164) has partially explained by some diffusion experiments the acidity of normal urine. He found that by placing in a diffusion apparatus a mixture of the mono-sodic (acid) and di-sodic (alkaline) phosphates of sodium, the acid phosphate passes through the membrane much more readily than the alkaline, so that while the fluid in the dialysor has an alkaline reaction, that without has an acid one. This is virtually what takes place in the kidney. The blood contains both of these phosphates of sodium, the di-sodic phosphate being constantly deprived of a part of its sodium by uric, hippuric, lactic, and other acids, which are produced by the metamorphosis of the nitrogenous tissues. The mono-sodic phosphate thus formed then readily diffuses from the blood to the urine, and imparts its acid reaction to that fluid, while the principal part of the di-sodic phosphate remains in the blood.—*Reviser's Note.*]



act in this way; further, all vegetable salts, which are converted in the body into carbonates and are eliminated as such in the urine (acetates, citrates, malates, and tartrates). All of these drugs, when they are taken in large doses as medicines, render the urine alkaline, and often in a very short time. Bence Jones found that 120 grains of dry tartrate of potassium dissolved in four ounces of water made the urine alkaline in thirty-five minutes; two hours later the alkaline reaction had disappeared again. Smaller doses, which are not sufficient to render the urine alkaline, at least diminish its quantity of acid.

Food acts in the same way, and according to the nature of its constituents sometimes increases the alkalinity of the blood and sometimes diminishes it. It is known that the urine of carnivorous animals is acid for this reason, and that of herbivorous animals is alkaline. A similar action of food on the urine is shown in man, though usually in a less degree, because his diet is in most cases a mixed one.

But certain processes in the organism also, results of the secondary metamorphosis, without doubt exercise an influence on the reaction of the urine by changing the alkalinity of the blood. The nature of these processes is, however, very obscure at present, and it is only by very difficult and complicated investigations that we can clear them up. In the meantime the following conditions may be designated as probable:

a. Bence Jones has pointed out that the acid reaction of the urine increases and diminishes inversely with the secretion of the acid gastric juice. He asserts that the urine is most acid at the time when the stomach contains no gastric juice, or when this secretion has been returned again to the body; and that, on the other hand, it becomes less acid or even alkaline in proportion as the acid gastric juice is separated from the blood.

Unfortunately, the experiments performed by Bence Jones to prove this point are not convincing. In these, as in almost all of his quantitative examinations of urine, the amount of acid is reckoned for 1,000 parts of urine and not for the hourly secretion, as should be the case if trustworthy conclusions are to be drawn from them. Experiments which were performed partly by myself and partly by others under my direction invariably showed that the greatest quantity of acid passed with the urine per hour was in the night, the least was during the hours be-



fore noon; while the quantity of acid in the afternoon hours (after the chief meal) was a mean between the two. These experiments, therefore, do not agree with the statements of Bence Jones, but they do not positively contradict them, since other circumstances may influence the amount of acid in the urine.

Theoretically Bence Jones's hypothesis appears to be very plausible: a quantity of acid is separated from the blood with the gastric juice, the blood becomes more alkaline, and consequently the urine secreted at this time contains less acid. It is possible, however, that the alkali which was combined with the acid of the gastric juice does not remain in the blood, but passes over into the bile, so that the alkalinity of the blood suffers no change through the secretion of the gastric juice, and consequently the secretion of the gastric juice has no influence on the acidity of the urine. Recent investigations of W. Roberts have confirmed the statements of B. Jones. (Compare § 127.)

b. According to the investigations of Liebig and others, the muscular juice is acid, or at least it becomes so immediately after being expressed. Now since the urine of carnivorous animals is rendered acid by the constituents of the meat which they take as food, it is probable that in man (and in animals) a part of the acid of the urine, perhaps the greatest part, is derived from the muscular juice produced by metamorphosis and passed into the blood, or, in other words, the acid of the urine is in part a product of the metamorphosis of the muscular tissue.

That this is the case is indicated by the observation which has often been made, that in herbivorous animals which generally secrete an *alkaline* urine, it becomes acid when they starve, that is, consume the constituents of their own bodies.

However, this is not the place to discuss these difficult theoretical questions. From the physician's standpoint the following are the chief points of interest in the reaction of the urine:

1. The urine has an *acid* reaction. This is the normal condition, and has only a negative value for the practitioner, since he determines from it the absence of certain diseased conditions. Further conclusions are obtained in this case, when the amount of acid has been accurately determined quantitatively (§ 127). A very acid condition of the urine may favor the formation of certain sediments or concretions, especially uric acid,

or it may give rise to an irritation of the kidneys and urinary passages.

2. The urine has a *neutral* or *alkaline* reaction. This condition is always of importance to the physician, and requires an accurate investigation. In such a case we must regard the following particulars :

a. The alkaline reaction may depend upon carbonate of ammonium (red litmus paper becomes blue when dipped in the urine, but after drying it becomes red again, and a glass rod moistened with hydrochloric acid and held over the urine develops a white cloud). This always comes (except in the rare cases where the carbonate of ammonium is directly eliminated with the urine) from the decomposition of urea in the already secreted urine; or,

b. The alkaline reaction depends upon a fixed alkali, potash, soda, or an alkaline earth (red litmus paper is made blue by the urine and remains so even after drying, and a glass rod dipped in hydrochloric acid and held over it does not show a white cloud). The cause in this case may be :

The medicinal use of caustic or carbonated alkalies, or of alkaline salts of the vegetable acids, or a diet rich in the latter, or alterations in the metamorphosis, which was briefly referred to above.

The answer to the question as to how far the physician must regard a neutral or alkaline condition of the urine, that is, more especially in reference to his prognosis and treatment, depends chiefly on whether this condition of the urine is temporary or permanent.

If the urine has only a transient neutral or alkaline reaction at a certain time of the day, more especially a few hours after eating, after certain kinds of food, or on certain days, it has a physiological but no practical signification.

If, however, the urine is frequently or permanently alkaline, important semiotic and practical conclusions may be derived from it, which are different in different cases :

1. The cause is a decomposition of the urea within the urinary passages. The diagnosis of these cases is made from the fact that the urine is ammoniacal, and contains mucus and crystals of ammonio-magnesian phosphate.

2. If the cause lies in the continued use of caustic alkalies,

their carbonates or vegetable salts, the diagnosis is self-evident from the above.

3. The cause consists in alterations of the metamorphosis. These are thus far only imperfectly understood; but we may designate as probable: arrest of the muscular metamorphosis, weakness of the nervous system, anæmia and chlorosis, defective nutrition, and general debility. One of the greatest services of Rademacher \* is that he called attention to the fact that a constantly alkaline urine is an iron affection, that is, translated into scientific language, requires the use of tonic remedies. Still, from what has been mentioned above, it is evident that this is true only in a limited sense, and, moreover, the pale color of the urine in such cases forms a surer indication for the careful observer that tonic remedies are indicated than the alkalinity of the urine, which is often absent in such cases.

The rational treatment of such conditions is frequently very difficult. The chief task is always to discover and combat the cause of the alkalinity. It is a very bad practice, and the result of erroneous chemical reasoning, to give acids in all cases in which the urine is alkaline. When the alkaline state of the urine depends on an irritation of the urinary passages, which is brought about by a too acid and irritating character of the urine with the formation of uric acid gravel, on the contrary, in addition to demulcent remedies, alkaline carbonates or acetate of potassium are the best remedies.

The assertion, which has often been repeated, that benzoic acid taken internally renders alkaline urine more quickly and certainly acid than other acids, has not been confirmed by the results of numerous experiments performed by me with reference to this point.

### III. THE APPEARANCE OF UNUSUAL (ABNORMAL) CONSTITUENTS IN THE URINE.

All changes of the urine which come under this head have a great practical importance, for in all cases we must infer the existence of diseased conditions. Every abnormal constituent which appears in the urine has its own signification; we shall,

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\* *Rechtfertigung der verstandesrechten Erfahrungsheillehre*, 2. Aufl., Bd. 2, S. 211, *et seq.*

therefore, immediately proceed to consider the various abnormal constituents.

### § 97. ALBUMEN.

A. The *detection* of albumen in urine has already been described in § 23. But since it is not always very easy, and certain precautions are required, and, moreover, physicians may very easily be led into error in testing for this substance by sometimes overlooking albumen when present, and sometimes wrongly considering it to be present when this is not the case, it appears best to return to the subject once more.

We detect albumen in the urine :

1. By adding *nitric acid*. When much albumen is present, an intense white turbidity is formed in it, or the fluid changes to a white pulp. In such cases no doubt can exist about the presence of albumen in the urine after this reaction. But the case is different when only a small quantity of albumen is present; the slight cloudiness which occurs may then be overlooked, or a cloudiness produced by the presence of other matters, such as urates, mucus, and the like, may be considered as due to albumen. It is best, therefore, to proceed with a certain caution in adding nitric acid.

As Heller has advised, a somewhat broad liquor glass is the best vessel to use in performing this test; it is two-thirds filled with urine, and a little nitric acid is allowed to flow down the side of the glass slowly and carefully, so that it may collect at the bottom. If albumen is present, a turbid zone sharply defined on the upper and lower surface is formed above the acid, which is not readily overlooked on account of the contrast; this process, therefore, may serve to detect the slightest traces of albumen in the urine. A cloudiness of the urine, depending on the presence of urates, may be produced by the nitric acid, but this cloudiness, when the test is performed as above, is sharply defined only on the lower surface toward the layer of acid, while above it pervades almost the whole urine in the form of cloudy streaks. An experienced person is able by this procedure to distinguish between the zones of albumen and urates when they occur together. It is observed that immediately above the clear layer of acid there is a cloudy zone of coagulated albumen sharply defined both on the upper and

lower surface; above this there is a zone of clear urine, and then a layer which is made cloudy by urates.\* (Compare also § 23, page 95, *et seq.*)

2. By *boiling* the urine, so that the albumen is coagulated, and, when much albumen is present, a flocculent coagulation is the result; when little is present there is a cloudiness only.

But this test may deceive us also; a cloudiness of the urine may result from boiling when no albumen is present. This cloudiness in the majority of cases is caused by the earthy phosphates; in very rare cases (in osteomalacia) it depends on the presence of a peculiar protein substance different from albumen.† Both these last-named turbidities are very readily distinguishable from that due to the albumen, since they disappear again after the addition of a little acid (acetic or hydrochloric acid), which is not the case with the cloudiness due to albumen. These two turbidities may, furthermore, be distinguished from each other by the fact that the protein substance is dissolved by caustic potash, but the earthy phosphates are not. The protein substance is also distinguished from albumen by the fact that it is not precipitated by nitric acid.

Albumen in urine, moreover, is not under all circumstances coagulated by boiling; for instance, not when the urine is alkaline. We must, therefore, always test the reaction of the urine before boiling, and, if it is alkaline, we must carefully neutralize it with acetic or nitric acid.

Sometimes, though very rarely, albumen is not precipitated even in an acid urine by boiling. This is the case when the urine contains a large quantity of free hydrochloric or nitric acid, each of which may form a compound with albumen which is soluble in both cold and boiling water. (Bence Jones.)

When the physician wishes to decide the question with certainty, whether a specimen of urine contains albumen or not, it is best to try both the nitric acid and the heat tests.

These reactions, however, only allow of the detection of that form of albumen which occurs most frequently in the urine, and which especially forms so-called albuminuria (serum albumen). Besides this, still other varieties of albumen may occur

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\* Heller's Archiv für Chemie und Microsc., 1852, p. 168, *et seq.*

† Heller in his Archiv, 1852, p. 167.

in the urine, all of which are not indicated by these reactions, but require special chemical tests for their detection and separation. For particulars on this point see below (II.).

B. What *significance* has the presence of albumen in the urine for the physician?

The answer to this question, which has occupied pathologists and physicians, is very difficult, and if we do not proceed very carefully, we run the risk of drawing false conclusions when the urine contains albumen, as has very frequently happened to physicians, many of whom are inclined to regard every albuminuria as indicative of a dangerous organic disease of the kidney (*morbis Brightii* in its broadest sense). The following points will assist us in considering the diagnosis and prognosis:

1. The albumen in the urine may depend on an organic disease of the parenchyma of the kidney, which is combined with its serious change and disorganization (exudation into the renal tubuli, alteration and separation of the epithelium—Bright's disease in the broadest sense; amyloid degeneration of the renal capillaries, etc.). This supposition becomes almost a certainty when casts are found in the urine at the same time, less of a certainty when only separated epithelial cells from the urinary tubules are found. (Compare § 116.) It is rendered probable by the simultaneous presence of dropsy, or when a large amount of albumen has been present in the urine for a long time, weeks or months. The prognosis in such a case is usually unfavorable. Still, a few apparently very bad cases running an acute course may completely recover, and chronic cases may last very long (for years) without seriously endangering the health or life.

2. The albumen in the urine may depend on a local disease of the uropoëtic system when Bright's disease does not exist.

When blood, blood plasma, or pus is mixed with the urine it contains albumen. In this case, however, the urine also contains, besides albumen, blood corpuscles, blood coloring matter, fluid or coagulated fibrine, and pus corpuscles. The diagnosis of these foreign constituents and their signification may be found in the following sections.

In rare cases the urine may also contain albumen from an abundant mixture with the spermatic fluid.\*

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\* Bence Jones, *Animal Chemistry*, 1850, p. 108.

But the urine may also contain albumen without this admixture from an irritation and hyperæmia of the kidneys, namely, passive hyperæmia, in which the capillaries of the kidney appear to be so modified that they allow a little albumen to filter through their walls into the urine. This is sometimes observed after the use of powerful diuretics, cantharides, etc., after ligation of the renal veins or of the aorta below the origin of the renal arteries, after the injection of a large quantity of water into the blood, and especially under conditions which increase the blood pressure in the renal vessels. Many diseases, without doubt, may have a similar action on the kidneys, and thereby render the urine albuminous.

3. But probably albumen may pass into the urine also on account of certain alterations in metamorphosis and especially in the blood, without local disease of the kidneys. But we know very little as yet of these relations and their mode of action; however, the following points may be laid down with more or less probability:

a. In that condition of the blood in which the serum becomes poor in albumen and rich in water (hypalbuminose, hydræmia) we sometimes see albumen appear in the urine.

b. When albumen in solution is injected into the blood of animals, or when they are largely fed with albumen, we sometimes find the urine albuminous, sometimes not. A further pursuit of these experiments by Corvisart, Schiff, Stockvis, Parkes, Pavy, and others has led to the opinion that certain forms of albumen pass through the walls of the renal vessels more readily than others, and it has been supposed, further, that certain modifications of the blood albumen, which are formed in disease by abnormal metamorphosis, may give rise to albuminous urine.

The experiments of Pavy\* indicate this. They show that the albumen contained in the urine does not always act in the same way on dialysis, and, moreover, it has different qualities from the albumen of the blood serum. Terreil† declares that in temporary albuminuria and in the beginning of Bright's disease the albumen in the urine possesses different characteristics

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\* *Lancet*, May, 1868.

† *Gaz. des Hôpît.*, 1868, 63.



from that in an advanced case of Bright's disease. In the first case, from the presence of paralbumen a precipitate produced by strong alcohol is dissolved again by a large amount of water, and potassio-cupric tartrate causes, especially when heated, a beautiful violet color. In a marked case of Bright's disease, on the contrary, the alcoholic precipitate is not dissolved again by water and the copper solution produces no violet color. Others (Gerhardt, Masing, Schultzen and Riess, Edlefsen) have found varieties of albumen in the urine of patients which differed from ordinary serum albumen: paralbumen, paraglobulin, peptone, etc. (Compare below, page 384, *et seq*).

A. Creitte \* has also communicated experiments on the action of serum albumen when injected into the blood. He found that, as a rule, an albuminuria was produced by it which was only transitory, but sometimes was accompanied by very bad results.

Whether in the cases of the separation of albumen considered under a and b, a visible alteration in the kidneys (hyperæmia and dilatation of the vessels, partial separation of the epithelium of the urinary tubules) precedes or not, cannot usually be determined. But this much is certain, that this affection of the kidney when it exists is only temporary; and consequently from the presence of albuminuria alone we cannot conclude that there is material alteration of the kidneys (so-called Bright's disease), but only when at the same time there are other signs, such as the presence of renal casts in the urine. It is self-evident, moreover, that we should only think of Bright's disease in those cases in which the urine has been constantly and for some length of time albuminous.

If we have reason to believe that Bright's disease does not exist, it remains to determine whether the albuminuria is dependent on an inflammation of the kidneys or on a change in the blood. The answer to this question naturally requires a further examination of the case, and is sometimes positive, but often only conjectural. It is usually of great value in reference to the prognosis and treatment, especially when it is a question whether we shall use diuretics or not.

The following suggestions may serve as hints in forming an opinion concerning many cases of albuminuria:

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\* Henle und Pfeuffer's Zeitschr. 86, p. 90, *et seq*.



Waldenström repeatedly observed the occurrence of albumen in the urine after the external or internal use of carbolic acid.

Hegar and Kaltenbach \* frequently, but not always, found the urine to be albuminous after the administration of chloroform.

E. Gerhardt† repeatedly observed that patients who frequently or constantly had a temperature of over 40° C. had albumen in their urine, if not in the ordinary form, at least in a form described by him as latent, which is not precipitated by boiling or on the addition of nitric acid, but is precipitated by alcohol (peptone).

H. Senator ‡ showed that several different albuminoid bodies occur in the urine, yet in different amounts under different conditions and in varying proportions to each other. Indeed albuminoid bodies occur in the urine which were not previously found in the blood, and, conversely, some are absent from the urine which are found in the blood. The albuminoid bodies of which we speak are :

1. *Globulin* or *paraglobulin* ; it is detected by diluting the albuminous urine with water until its sp. gr. is 1.002 or 1.003, and conducting carbonic acid gas into it for two or four hours. The cloudiness which is thus produced forms usually, but not always, after one or two days, a milky precipitate, which dissolves again on adding very dilute hydrochloric acid or a solution of chloride of sodium and concentrated acetic acid. Cases of amyloid degeneration of the kidney showed the greatest amount of paraglobulin, and cases of acute nephritis contained a large amount of it. On the other hand, very little or no paraglobulin was found in chronic diffuse nephritis. In catarrh of the bladder the urine always contained paraglobulin, besides a relatively scanty amount of albumen.

2. *Alkali albuminate*, that is, a body which is obtained from blood serum after precipitating the paraglobulin with acetic acid, either does not appear in the urine at all, or only in very slight traces.

3. *Peptone* (precipitable with alcohol after separating the other varieties of albumen by boiling) is contained in small

\* Virchow's Archiv, 49, p. 437, *et seq.*

† Deutsches Archiv f. klin. Med., 1868, v., p. 212, *et seq.*

‡ Ueber die im Harn vorkommenden Eiweisskörper, etc., in Virchow's Archiv, 1874, Band 60, p. 476, *et seq.*

amount in every albuminous urine, and, according to Gerhardt (see above), under certain circumstances occurs in urine which contains no albumen coagulable by heat.

Sometimes a *quantitative* estimation of the albumen separated by the urine is desirable, especially in cases where we wish to know how much is thus removed from the body, and whether an essential impoverishment of the blood is to be feared from this cause or not. (Hypalbuminosis, hydræmia).

In order to make such quantitative estimations of the albumen practically serviceable to the physician, we mention the following considerations, and we must not only determine the percentage of albumen in the urine, but must also calculate it for a given time, preferably twenty-four hours.

The quantity of albumen which is passed with the urine in albuminuria varies greatly from a minimum (less than one grm. daily) to 20 and even 30 grm. of dry albumen in twenty-four hours. Keeping these facts in mind, the loss of albumen with the urine may be considered in the following categories:

It is *insignificant* and has hardly any influence on the composition of the blood and metamorphosis, when the amount separated is less than 2 grm. in twenty-four hours.

The loss is *moderate* when the daily quantity averages 6 or 8 grm.

The loss is *considerable* when it exceeds 10 or 12 grm.

20 grm. and more of albumen in twenty-four hours is an unusually large quantity and belongs among the exceptions; it rarely lasts long at this height. 28.3 grm. of albumen was the maximum quantity which I have thus far seen pass off with the urine in twenty-four hours in a large number of observations.

If we seek to obtain an approximate idea as to the action of such a loss of albumen on the quality of the blood, and especially whether it can bring about a morbid diminution of the albumen in the blood serum (hypalbuminosis, hydræmia), we must proceed as follows: We will assume the most unfavorable conditions, in which the serum constitutes only about one-half of the whole amount of blood, and according to which an adult possesses about 6,000 grm. of blood serum containing 8 per cent., in all only about 480 grm. of albumen. Moreover, if we suppose that as long as the albuminuria lasts, no albumen is formed from the protein bodies which are taken as food, and also, as

is scarcely probable, none from the hæmatoglobulin of the broken-up blood corpuscles. If now 10 grm. of albumen are passed daily on an average, in ten days 100 grm., the amount of albumen of the blood serum sinks to 380 grm., and the relative amount in the blood serum is diminished from 80 to 64 parts in a thousand, which corresponds to a tolerable degree of hydræmia. After twenty-six days such an albuminuria would have diminished the amount in the blood serum to 37 parts in the thousand—a number which nearly corresponds with the minimum amount of albumen in the blood serum in hydræmia observed by Becquerel and Rodier. These considerations show how, under the above conditions, a high degree of hydræmia may be produced in a relatively short time by an abundant albuminuria. Experience teaches us, however, that the action of an albuminuria on the quality of the blood is only rarely so considerable, except in a few very acute cases accompanied by fever, and in patients whose appetite and digestion are lost. When we remember that 100 parts of meat contain about 15 or 20 parts of protein substances, which, if the digestion is good, are almost wholly converted into a soluble form of albumen, and pass into the blood, under favorable circumstances a loss of 10 grm. of albumen daily may be replaced by the additional ingestion of about three ounces of meat or a corresponding quantity of other food containing protein; and, in fact, I have often seen in patients with a fair digestion and without fever, who were well nourished, a moderate degree of albuminuria last for months or even years without causing a perceptible hydræmia or symptoms which pointed toward it.

The methods which are used to determine the albumen in the urine quantitatively were described in § 75.

A. Stscherlakoff and Chomjakoff\* have undertaken comparative examinations as to the accuracy of these different methods. According to these authors the estimation of albumen by coagulation and weighing (compare page 293, *et seq.*) does not give perfectly accurate results, because all of the albumen is not precipitated by it. When the urine contains 0·5 per cent. of albumen, from four to eight times as much albumen remains dissolved as is precipitated. When it contains 1 per cent., that

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\* Deutsches Archiv f. klin. Med., 1870, viii., p. 218, *et seq.*

which remains dissolved nearly equals that which is precipitated. When there is more than 2 per cent. of albumen, about one-third of it remains in solution.

The estimation of albumen from the difference of the sp. gr. before and after coagulation of the albumen by the method of Lang and others (compare page 297, 3) gives very inaccurate results.

On the other hand, the optical determination of the albumen by the polariscope (compare page 296, B) is the most accurate, and at the same time the simplest and quickest method.

P. Liborius \* has also undertaken comparative experiments as to the accuracy of the different methods of determining albumen. According to him its precipitation by alcohol, by which peptone is also obtained, gives the most accurate results known at present.

For mere approximate determinations of the amount of albumen in the urine, when the physician only wishes to know whether the separation of albumen in albuminuria is inconsiderable or large, and especially whether it increases or diminishes, the following procedure, which does not require extensive apparatus, may be adopted :

Test tubes of the same diameter are to be chosen in precipitating the albumen from the urine by boiling or adding nitric acid, and the precipitate of albumen is allowed to remain at rest for twelve or fourteen hours. The relative amount in comparison with the quantity of urine used in the experiment may thus be easily approximately estimated. If the tests of the urine of different days are preserved, their amounts of albumen may be compared, and we may easily see whether it increases or not. This estimation is more exact, when we use, instead of test tubes which are rounded at the bottom, not too narrow glass tubes with a diameter of from  $\frac{1}{2}$  to  $\frac{3}{4}$  of an inch and an even bore, which are closed below by a tightly fitting cork cut off squarely, and into which the boiled urine is poured. If the albumen precipitate has completely settled in these after twelve or twenty-four hours, we can estimate with the aid of a measure held near the tube how many tenths or hundredths of the whole

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\* Beiträge zur quantit. Eiweissbestimmung im Deutsch. Archiv f. klin. Med x., 1872, p. 819, *et seq.*

quantity of urine the precipitate of albumen occupies. But we must not forget that only the *relative* and not the *absolute* quantity of albumen contained in the urine is learned in this way. Apart from this also such calculations always remain somewhat uncertain; for according as the albumen coagulates on boiling in coarser or finer particles, and according to the specific gravity of the urine which remains behind, the precipitated albumen sometimes assumes a larger and sometimes a smaller volume, and experiments, in which the albumen has been determined at the same time by weight and by volume, have shown me that in estimating it according to the latter method errors of 30 and even 50 per cent. may be made. Therefore the statements of some of the French pathologists with reference to the separation of albumen in albuminuria under the influence of various agencies, as far as they are founded on the estimation of the albumen by volume, must be received with great caution.

#### § 98. FIBRINE.

Fibrine under various circumstances may appear in the urine sometimes coagulated and sometimes in solution.

*Coagulated* fibrine appears either in large particles visible to the naked eye, as blood coagula, which cannot be mistaken (see the following section), or, more rarely, in the form of colorless, sometimes solid, sometimes gelatinous fibrinous coagula; or again in very small particles visible only with the microscope in the form of so-called urinary casts or cylinders. (See Urinary Sediments, § 116.)

*Dissolved* fibrine in the urine forms the so-called coagulable urine, which is characterized by the formation of fibrinous coagula in it after some time (generally several hours after it has been passed); sometimes these only cover the bottom of the vessel and form a sort of coherent sediment in the lower part of the urine; sometimes it occupies the whole mass of urine and transforms it into a completely gelatinous mass. This coagulable urine is seen in this country very rarely, but outside of Europe it is met with more frequently (Brazil, Isle de France, etc.).

The fibro-gelatinous mass which forms may very readily be confounded with that which occurs much more frequently with

us, and which is formed by the action of carbonate of ammonium upon the pus corpuscles contained in the urine, as often happens in catarrh of the bladder. (Compare § 113 and § 114.)

Coagulable urine sometimes contains blood also. In such cases we cannot be sure that the urine contains fibrine as well as blood, unless the fibrinous coagulum is so large that it cannot be ascribed to the presence of the blood alone.

I saw such a case in a woman who was suffering from Bright's disease. Here, for a long time, a very pale-red fibrinous coagulum containing numerous pus corpuscles and a few blood corpuscles was regularly formed at the bottom of the glass some hours after the urine was passed. The blood corpuscles, however, were far too few to indicate that the blood which they represented could have yielded the whole of the fibrinous coagulum.

*Importance.* Fibrine in the urine, whether dissolved or coagulated, always indicates that at some part of the uropoëtic system an exudation of a fibrinous fluid (blood plasma) has occurred. In most cases this fibrine comes from the kidneys, but it may arise from some other part of the urinary passages.

## § 99. BLOOD IN THE URINE.

(Blood Corpuscles. Blood Coagula.)

*A. Detection.* The urine has the color of blood, and under the microscope shows the characteristic blood corpuscles. (See § 51.) If the quantity of blood is very small, we cannot be sure of finding the blood corpuscles, unless the urine has stood a long time. They then become deposited as a red sediment on the bottom. In this way we may recognize even a very small amount of blood with the unaided eye: should any doubt exist as to the nature of the sediment, it must be cleared up by a microscopic examination.

The blood may coagulate, if the quantity is rather large, either within the urinary tract, when the large blood coagula may stop up the urinary passages, causing dysuria, strangury, or retention of the urine, sometimes giving rise to the formation of urinary calculi even, or the coagulation of the blood may take place in the urine after it has been passed. (Compare § 98.)

**B. Importance.** Blood corpuscles or blood coagula in the urine always indicate that a hæmorrhage has occurred somewhere in the urinary passages. The causes of such a hæmorrhage and its results are very various, and this is not the place to describe at length all of the possible causes which may give rise to it. The following considerations will serve as guides in the examination :

When the urine contains *very much* blood, it usually comes from the pelvis of the kidney, the ureters, or the bladder, rarely from the kidneys themselves. Sometimes the cause of the hæmorrhage depends on a general scorbutic condition, the diagnosis of which presents no difficulties to the careful physician.

With this exception hæmorrhages from the pelvis of the kidney and the ureters is most frequently caused by renal calculi, more rarely by ulceration of these parts from other causes. In such cases, in addition to the hæmorrhage there usually exists an inflammation of the pelvis of the kidney and of the ureters (pyelitis) ; the urine contains, in addition to the blood, pus corpuscles also, sometimes fragments of calculi or gravel; there is pain in the region of the kidneys and in the course of the ureters. This set of symptoms usually establishes the diagnosis.

If pain is wanting in the region of the kidneys or in the course of the ureters, the source of the hæmorrhage is probably to be found in the bladder. The causes may be : hyperæmia (so-called vesical hæmorrhoids), vesical calculi, erosions, and ulcerations of the mucous membrane of the bladder, or serious organic lesions of the bladder, especially cancer, which has become softened. The other symptoms of disease of the bladder which are present in addition to the bloody urine in such cases, generally enable us to readily discover the source of the hæmorrhage, and a careful examination and continued observation, as a rule, will give us a clue to the nature of the disease.

Sudden or temporary symptoms of disease of the bladder (dysuria, ischuria) occurring without premonitory symptoms may arise when the hæmorrhage has taken place, not in the bladder, but in the pelvis of the kidneys or in the ureters. This happens when the blood which has found its way to the



bladder coagulates there, and thus occludes the urethral orifice, or when blood coagula are washed out of the ureters into the bladder and in the same way render micturition difficult or impossible.

If the quantity of blood in the urine is small, and there are symptoms present which indicate disease of the urinary passages, it is probable that the blood has come from the parenchyma of the kidneys, and especially from the vessels of the Malpighian corpuscles, and we have to deal with a disease which belongs under the large class of so-called Bright's disease. In such cases when the hæmorrhage is not very transitory, the urine usually contains besides blood, fibrinous casts, or pus corpuscles and granule cells, whose presence not only strengthens the diagnosis, but also sometimes enables us to diagnosticate with more or less probability a certain form of kidney disease.

In all cases of hæmorrhage in the uropoëtic system the physician must not be contented with simply diagnosticating the seat and cause of it, but must also try to determine the possible consequences for the purposes of prognosis.

The following considerations may be of service in this respect:

A hæmorrhage from the urinary passages is only rarely so considerable that it directly causes an essential diminution of the blood corpuscles in the body, and thereby brings about anæmia or oligocythæmia.

More frequently the evil consequences arise as follows: The effused blood coagulates wholly or partially in the urinary passages and occludes the ureters or urethra, and thus hinders the evacuation of urine, or these coagula may give rise to the formation of permanent concretions (urinary calculi) in the urinary passages. Even in those cases in which the quantity of effused blood is very slight, small coagula may become the nuclei of future urinary calculi.

In forming the prognosis of a hæmorrhage, in addition to these possible results we must always take into account the results of the process which gave rise to the hæmorrhage: the affection of the kidney, the pyelitis, the disease of the bladder, etc.

Every specimen of urine which contains blood corpuscles



must also contain fibrine and albumen, because these substances form integral constituents of the blood. Only a careful investigation based on approximate quantitative determinations of these three constituents of the blood can decide whether the whole quantity present in the urine is derived from the blood which has been effused, or whether in addition to the blood there has been an exudation of fibrine or of albumen. (Compare § 98.)

#### § 100. DISSOLVED BLOOD. DISSOLVED HÆMATOGLOBULIN.

(Hæmoglobin and Methæmoglobin.)

Sometimes the urine has a bloody color or is reddish brown, brownish black or even inky black, and yet no blood corpuscles can be detected in it by the most careful microscopic examination. If, however, such urine be boiled either alone or after the careful addition of a little acetic acid, a more or less abundant brownish-red coagulum forms in it, which is precisely similar to that which blood diluted with water gives on being boiled. If this coagulum is then boiled with alcohol which contains sulphuric acid, the fluid becomes colored reddish brown by dissolving hæmoglobin. We can thus, especially when the spectral analysis is employed, prove with certainty the presence of dissolved blood pigment in the urine, and at the same time discover whether it consists of original hæmoglobin, of altered hæmoglobin (methæmoglobin), or of hæmatin. (See § 51.)

Such urine is occasionally met with in diseases which are associated with what is called a dissolved state of the blood, as in scurvy, in putrid and typhus fevers, in malignant remittent fever, and after the inhalation of arseniuretted hydrogen gas.\*

*Examples.* A., a young man, suffering from a severe attack of typhoid fever, passed at the height of the disease, for several consecutive days, urine of a blood-red color, which under the microscope showed no traces of blood corpuscles, but on boiling gave an abundant coagulum of hæmoglobin. After a few

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\* J. Vogel im Archiv d. Vereins f. gemeinsch. Arbeiten., Band 1, Heft 2, p. 200.

days this state of the urine disappeared, and the patient recovered slowly though perfectly.

X., in perfect health, while performing an experiment, inhaled a gaseous mixture, which besides atmospheric air contained hydrogen mixed with some arseniuretted hydrogen. He became momentarily ill, but soon recovered. The urine which he passed a short time afterward was inky black; it contained no blood corpuscles, but on boiling yielded an abundant coagulum of hæmoglobin. This condition of the urine lasted about twenty-four hours.

Also, some smelters, who inhaled arseniuretted hydrogen in the extraction of silver from the ore and suffered from poisoning in consequence, three of the nine cases affected proving fatal, passed bloody urine.\*

A dog which was allowed to inhale a large quantity of arseniuretted hydrogen experimentally, also passed a urine of a dark blackish-brown color containing a large amount of hæmoglobin.

Recently, since the operation of transfusion has been performed repeatedly, a number of the patients operated upon have also passed dissolved blood-coloring matter with the urine.†

The passage of hæmoglobin with the urine in such cases may perhaps be explained in the following way: The blood corpuscles are being constantly decomposed in the body by the metamorphosis of tissue, and hæmoglobin is thereby set free. When the metamorphosis takes place normally, it is probable that this hæmoglobin which is set free, always only in very small quantity, is further decomposed: the globulin is finally removed from the body in the form of urea and uric acid; the hæmatin also undergoes further change, and is probably separated from the body finally as urinary and biliary coloring matter, so that in the normal course of metamorphosis, hæmoglobin never appears in the urine. When, however, in pathological processes very large quantities of blood corpuscles are at once decomposed, the amount of hæmoglobin present in the

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\* Trost in Eulenberg's Vierteljahrsschr. f. gerichtliche Medicin u. öffentl. Sanitätswesen, Band 16, p. 269, *et seq.*

† Oehme, Sitzungsbericht d. Dresdner Gesellsch. f. Natur. und Heilkunde v. 11. April, 1874. See also Landois, Centralbl. f. d. medic. Wissensch., 1873, No. 56 and 57.

blood is so great that the whole of it cannot undergo the normal change, and a part of it then apparently passes unchanged into the urine, just as happens with other matters which do not usually appear in the urine, as, for example, sugar, biliary substances, and perhaps also albumen when present in the blood in excess.

This is apparently confirmed by the experiments of Ponfick,\* which showed that *small* quantities of hæmoglobin introduced into the vascular system of animals are decomposed by metamorphosis and disappear, while *large* quantities give rise to hæmoglobinuria and are in part separated unchanged by the kidneys.

*Importance.* The presence of hæmoglobin in the urine is important to the physician in two ways.

1. It indicates that there has been an excessive pathological decomposition of blood corpuscles. Under this head there are two sorts of cases which we must distinguish in practice :

a. The cause of the decomposition of the blood may be a *temporary* one, in which case the evil results are confined to the loss of a greater or less quantity of blood corpuscles ; the prognosis is favorable, as in the examples given above.

b. The cause of the decomposition of the blood may operate *permanently* ; a peculiar dissolution of the blood is thereby brought about which endangers life. The prognosis is unfavorable or at all events doubtful. It is seen in cases of severe scurvy, in typhus with dissolution of the blood, in septic fevers, etc.

2. We know from the observations of Meckel, Heschl, Freichs, and particularly from the beautiful experiments of Jul. Planer,† that in certain cases, and very probably in those cases in which a large amount of hæmoglobin is set free, granular pigment collects in the blood and may produce serious results by obstructing the capillary blood vessels, especially in the brain (melanæmia). It, therefore, appears advisable to examine the blood microscopically in such cases for any deposits of pigment which may occur before giving the prognosis. In such

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\* Virchow's Archiv, Band 62, p. 323, *et seq.*

† Ueber das Vorkommen von Pigment im Blute, Zeitschr. der Wiener Aerzte, 1854, p. 127 and 280. See also : Oppolzer, Wiener med. Wochenschr., 1860, 25 and 26 ; Mettenheimer, Würzburger med. Zeitschr., 1862, p. 1, *et seq.*

cases of melanæmia collections of pigment sometimes occur in the urine. (See § 116, p. 437.)

### § 101. FAT.\*

Our knowledge concerning the occurrence and signification of fat in the urine is still very incomplete. We do not know with certainty how often, in what quantity, and under what conditions it appears in normal urine : and the little which has hitherto been ascertained of its occurrence in pathological cases also appears unsatisfactory. The subject, therefore, requires further investigation ; however, what is already known indicates that the occurrence of fat in the urine promises to be of importance in the recognition and prognosis of many pathological conditions, especially of fatty degeneration of the kidneys.

*A. Detection.* To ascertain the presence of fat in the urine we resort to the process given in § 33. It is best to proceed as follows :

1. Sometimes we are able with the unaided eye to see fat drops in the urine similar to those which are seen floating on soup. These must be further tested by the very simple expedient of ascertaining whether the greasy spots which they make on paper remain after the paper has been dried. In all such cases, however, the physician must first assure himself that the fat in the urine is not accidental before he admits its existence—that it has not become mixed with the urine from unclean oily or fatty urine glasses, chamber vessels, medicine glasses, etc. This is a source of error which is far from uncommon.

2. In other cases the fat is recognized by the microscope. It appears in the form of drops or granules familiar to all microscopic observers, either free or enclosed in cells, masses of exudation, fibrinous casts, etc. To find them we must either seek on the surface of the urine, where free fat drops usually float on account of their light specific gravity, or at the bottom of the urine when the fat is enclosed in cells or coagula which form sediments.

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\* C. Mettenheimer, *Archiv f. gemeinsch. Arbelten*, Band 1, Heft 8, p. 374. A. G. Lanz, *De Adipe in Urina*, Dorpati, 1851. L. Beale, *London Microsc. Journ.*, January, 1853, 1, 2. Schmidt's *Jahrbuch.*, 1873, 7, p. 7. Kletzinsky, in Heller's *Archiv*, 1852, p. 287.

3. But the fat may be in such a minute state of division in the urine that it cannot be recognized even with the microscope. Then there is nothing left but to test the fat chemically as described in § 33, C, and § 82.

B. *Importance.* As far as we can judge at present, fat in the urine, when not of mere transitory occurrence, and when it lasts a considerable time, is of importance to the physician chiefly from the fact that its presence leads to the suspicion of a fatty degeneration of the kidneys, which may exist alone (fatty kidney), or may be associated with contraction of the organ, as in one of the various forms of so-called Bright's disease. In the last case the formation of fat occurs either in the secreting cells of the kidney (epithelium of the urinary tubules), or it arises from the fatty metamorphosis of exudations deposited in the kidneys.

It is not improbable, however, that fat in the urine may depend on other causes besides those mentioned here :

Upon a fatty degeneration of the epithelial cells of the ureters and the bladder.

Upon an excessive amount of fat in the blood, which might possibly occasion the passage of fat into the urine without a coëxistent fatty degeneration of the parenchyma of the kidney.

Thus Bérnard sometimes, though not always, saw fat appear in the urine of dogs who were fed on a very fatty diet.

For a more accurate study of these relations it will usually be necessary to determine the amount of fat in the urine *quantitatively*, either by an approximate estimation or, more accurately, by chemically extracting and weighing the fat which is passed in a given time—say twenty-four hours. Such a quantitative determination of the fat should be carried out according to § 82, or better still by Kletzinsky's method. He first boils the evaporated urine with alcohol, to which a couple of drops of acetic acid have been added, then evaporates to dryness again on the water bath and afterward extracts with ether. By this process the organic matter is better prepared for the subsequent removal of the fat by ether, and any *saponified* fat which may be present is deprived of its alkaline base and incorporated with the ethereal extract. Such estimations of fat, however, are troublesome, and require much time for their performance. Thus far only a few such investigations

have been made, and I know of none in which the quantity of fat separated in a definite time, say twenty-four hours, has been reckoned. Therefore, we have, thus far, no means of comparison.

The following experiments, in the meantime, may serve to aid us :

Kletzinsky found in the urine of different persons who suffered from Bright's disease the following quantity of fat in 1,000 parts of urine : 0·24—0·26—0·28—0·25—0·37—0·48—1·27.

Beale, on the other hand, found in one case 14 parts of fat in 1,000 parts of urine.

So-called *chylous* urine (see page 142) contains more or less fat in suspension, which gives it a milky appearance, and in addition to albumen, it frequently contains fibrine, and lymph and blood corpuscles. Lewis declares that at times there is a peculiar entozoon present also. (See § 118.) The discharge of such urine—called, also, *galacturia*—is only rarely observed in Europe ; on the other hand, it is observed with tolerable frequency in some of the tropical countries (East and West Indies, Isle de France). It is not yet explained how this disease, which often lasts a long time, originates.\*

Recently I had an opportunity, through the kindness of Dr. W. Harnier in Wildungen, to observe a very interesting case of well-marked galacturia, which originated, not in the tropics, but in Germany. The patient, a young man, for two years and a half had passed, almost without exception, a perfectly opaque urine of white color, which exactly resembled in appearance milk which contains a good deal of fat. The turbidity depends wholly on fat, which is, for the most part, very finely granular, and only has a few large fat drops like those in milk. The urine is cleared up by shaking with ether, and an abundant residue of semi-fluid fat remains behind after the ether is evaporated. The urine, moreover, contains a large amount of fibrine, which coagulates partly after the urine is passed, and partly while still within the urinary passages, and in the latter case the coagula are sometimes large and can only be passed through the urethra with a good deal of trouble. The urine contains only a trace of albumen. When the patient fasts, and at the

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\* Concerning this subject see, besides a tolerably copious foreign literature, Ackermann, *Deutsche Klinik*, 1863, 28, *et seq.*, and Eggel, *Deutsches Archiv f. klin. Med.*, vi., p. 424, 430.

same time drinks much water, the milky character of his urine temporarily disappears.

### § 102. BILIARY PIGMENTS.

The bile pigments which occur in urine and the process required to detect them have been studied in § 28.

*Importance.* In rare cases traces of bile pigments have been found in the urine of persons in perfect health, particularly in the hot season of the year.\*

Bile pigments are found in large quantities only in jaundice (icterus), and after phosphorus poisoning.

Their presence may be thus explained: The natural passage of the bile from the liver into the intestine being, for any reason, impeded or arrested, they get into the blood by absorption. The biliary pigments having been accumulated in the blood are separated from it with all of the secretions, but most particularly with the urine. It is very doubtful whether a *primary* accumulation of bile pigments in the blood can occur, that is, whether they can pass directly into the urine from the blood without having previously formed a constituent of the bile.

The idea originating with Frerichs, that the biliary pigment which is so abundant in icteric urine is derived partially from a decomposition of the biliary acids into biliary pigments in the blood, has not been confirmed.

The presence of bile pigments in the urine has no great diagnostic value, since we are usually able to recognize jaundice by other signs. In cases in which, owing to the slight yellow color of the skin, conjunctiva, etc., the diagnosis of jaundice is doubtful, the detection of the bile pigments in the urine may confirm it.

Biliverdin and biliprasin generally prevail in the urine in jaundice. This indicates that the greater part of the biliary pigment in icterus undergoes a change during its absorption, or after it has reached the blood, or while it is passing into the urine.

### § 103. BILIARY ACIDS.

The biliary acids which occasionally appear in the urine (cholic acid, glycocholic acid, choloidic acid, and their deriva-

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\* Scherer, Ann. d. Chem. u. Pharm., Band 57, p. 180-195.



tives, such as cholonic acid), may be detected by the methods given in § 29 and § 83, and may be, at least approximately, determined quantitatively.

Recently they have often been found in pathological urine, though always only in small quantity, especially in icterus and acute atrophy of the liver, by Kühne,\* Neukomm,† and Hoppe-Seyler.‡ Still their importance to the practitioner is slight, since it is rarely the case that important conclusions can be drawn from their presence or absence in reference to the diagnosis of a case of disease, or to assist in forming any other opinion concerning it. The presence of biliary acids in the urine is of practical importance only by indicating an accumulation of these acids in the blood, which may be dangerous when it is considerable, since they have a paralyzing influence on the nervous system, and more especially on the cardiac nerves. (Gerhardt.)

In the meantime the following points may be mentioned in reference to this subject:

Under normal conditions a considerable quantity of cholic acid is constantly being poured into the intestines with the bile. By far the greater part of it is absorbed again and passes back into the blood; here the cholic acid is altered in a manner not fully understood, and disappears as such. If this change does not go on in the blood, so that the cholic acid accumulates there, then a portion of it may appear in the urine. As yet we do not know the conditions which prevent the disappearance of cholic acid in the blood, and favor its appearance in the urine. When we have learned these conditions better, we shall be able to determine fully the diagnostic and prognostic value of the presence of cholic acid in the urine. We may, however, deduce a few conclusions from what is already known of these conditions as follows:

It is not altogether inexplicable why we find, as a rule, only a little cholic acid in the urine in cases of icterus, where the urine is loaded with biliary coloring matters. When the flow of bile into the intestines is arrested, the bile pigment, whose normal avenue of exit from the body with the fæces is closed, must take an unusual course; it is in part evacuated with the

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\* Virchow's Archiv, 1858, p. 810, *et seq.*

† Archiv f. Anat. und Phys., 1860, p. 364, *et seq.*

‡ Virchow's Archiv, 1862, p. 1, *et seq.*



urine. The cholic acid, on the other hand, passes normally in great part back again into the blood and there disappears; and since in icterus no change takes place in this respect, we can readily understand why, as a rule, in this disease we find much biliary pigment and little or no biliary acids in the urine.

Moreover, as the disappearance of the biliary acids takes place in the blood and not in the liver, we should not, as a rule, expect to find them in diseases of the liver, but in those diseases of the blood in which the normal decomposition of the biliary acids in the blood is impeded or arrested. We might expect that these acids would be found only in the urine in those diseases of the liver which are accompanied by an increase of the biliary secretion, and as the result of which so large a quantity of biliary acids accumulates in the blood that their normal transformation is not completely accomplished.\*

#### § 104. SUGAR.

To detect sugar in the urine we must proceed according to § 25, E. If the urine contains a large amount of sugar, its detection presents no difficulty to one who is a little skilled. The dark brownish-red color which saccharine urine assumes when treated with potassic hydrate and heated to boiling for a time is sufficient proof. The further test with sodic or potassic hydrate and cupric sulphate, as well as the tests with bismuth and indigo-carmin, will serve to confirm it.

Sometimes the urine also contains *alkapton* (see § 26) and *brenzcatechin* (see § 39). These cases, which are probably rare, and whose etiology is still unexplained, have no clinical importance, but they may lead to a false conclusion that sugar is present when this is not the case, from the great resemblance of the reactions caused by their presence in the urine to those caused by sugar. It is only by the reduction of nitrate of bismuth, the odor of caramel on boiling with potassic hydrate, and the fermentation test, that we can detect the presence of sugar in the urine when these substances are also present.†

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\* For further particulars on this head, see Huppert (Archiv d. Heilk., 1864, p. 236, *et seq.*), and Ernst Bischoff (Henle u. Pfeuffer's Zeitschr. f. rat. Med., 1864, p. 125, *et seq.*).

† Compare Dr. P. Fürbringer, Berliner klinische Wochenschrift, 1875, No. 24.

In cases where the tests above mentioned give no decisive results, we may be sure that the urine in question contains no very considerable quantity of sugar, and this suffices almost always for the purposes of the physician. Occasionally, however, we may wish to know whether in such a case the urine is perfectly free from sugar or not, and whether it contains a very small quantity, or a mere trace of it. To answer this question with certainty is difficult and requires time. We must then employ all of the precautions which have been described on page 109, *et seq.* (preparation of an alcoholic extract of the evaporated urine, of a saccharate of potassium, etc.).

To obtain an accurate *quantitative* analysis of the sugar in a specimen of urine, we must proceed according to § 70. The methods of analysis described there, however, are rather complicated, with the exception of the optical method, and cannot, therefore, be easily employed by the physician, but, as a rule, must be entrusted to the chemist. In order to learn accurately the progress of the secretion of sugar, we must ascertain the quantity of sugar formed in a given time ( $x$  grms. of sugar in an *hour*, for example, etc.).

Comparative trials of the accuracy of the different methods employed to determine quantitatively the sugar in the urine (the oxide of copper test, fermentation test, and that by means of the polariscope) have been made by Wicke and Listing.\*

Attempts have also been made to determine the quantity of sugar in diabetic urine from the specific gravity, and for this purpose tables have been drawn up which are said to show how much sugar urine of a certain specific gravity contains. This method is quite extensively used in England, but is very inaccurate and cannot be employed even for approximate determinations, as Bence Jones† has shown.

On the other hand, W. Manassëin‡ found that Roberts' method of determining the quantity of sugar from the difference in the specific gravity of the urine before and after fermentation gave quite serviceable results. (Compare page 277.)

Since the methods of determining the quantity of sugar in a specimen of urine as described above are difficult and tedious,

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\* Henle u. Pfeuffer's Zeitschr., Neue Folge, Bd. 6, Heft 3.

† Med. Times and Gazette, Feb. 4, 1854.

‡ Deutsches Archiv f. klin. Med., 1872, x., p. 73.

I have frequently employed another process instead, which is quite sufficient for the purposes of the physician, who, as a rule, only wishes to know *about* how much sugar a diabetic urine contains, and more especially whether the quantity has increased or diminished. This process is founded on the fact that saccharine urine when boiled with potassic hydrate assumes a yellowish-brown color, and that from the intensity of this color the quantity of the sugar may be determined by the aid of a color scale in the same way that the coloring matter of the urine is determined.

The best way is to proceed as follows: A weighed amount (about 2 grm.) of well-dried grape sugar is dissolved in 40 or 50 cc. of water, about double its volume of a tolerably concentrated solution of potassic hydrate is added, and the mixture boiled 10 or 15 minutes. After cooling, the fluid, which has become dark brown, is treated with water until 1 cc. of it corresponds to 10 mgrm. of sugar. From this original fluid a scale of colors is prepared. For not very exact investigations a scale of a few members is sufficient, and we may use ordinary test tubes of as nearly as possible equal diameter. We fill the first one with a fluid consisting of one part of the original fluid and nine parts of water, so that 10 mgrm. of sugar are contained in 10 cc. of the fluid. The second tube is half filled with the fluid first used and then an equal quantity of water is added; we then obtain a member of the scale in which 5 mgrm. of sugar are contained in 10 cc. A third, fourth, and fifth test tube are filled with fluids, 10 cc. of which correspond to 3, 2, and 1 mgrm. of sugar respectively, etc. If we prepare a scale of 10 or 12, members, and select large glasses of as nearly equal diameter as possible and having a capacity of  $\frac{1}{2}$  to 1 lb., we can arrive at a very accurate determination. When we have prepared such a scale, a measured quantity of the urine to be tested is boiled (when the urine is very saccharine 5 cc., when it contains but a little sugar 10 cc.) with double its volume of a solution of potassic hydrate; after cooling it is placed in a glass vessel corresponding in form and size to those of the scale, and water is added to it until its color corresponds to that of one of the members of the scale. We may now from the known quantity of the sugar contained in that member of the scale very readily reckon the quantity of sugar in the urine. This method

is very convenient (it requires only a few minutes to perform it), and is, therefore, especially adapted for clinical purposes. The scale itself does not keep long, it is true, but the original fluid when preserved in a cool, dark place may be kept a long time, and a new scale may be quickly prepared from it. In the rare cases in which the urine contains large quantities of alkapton or brenzcatechin (see page 400), this method is naturally not applicable, since these substances also color the urine brown when treated with potassic hydrate.

*Importance.* It is still very difficult at present to explain the cause of the occurrence of sugar in the urine. It, therefore, appears advisable to keep in mind the facts which are of most importance to the practitioner.

From the standpoint of the physician two points are to be discriminated:

1. In the one case the urine not only contains sugar in large quantities, but it is for a long time constantly present (only when fasting do such persons sometimes pass a urine which is free from sugar.)

2. In the other case the urine contains only traces of sugar, or the sugar is present merely temporarily, or for a short time, or contains a considerable amount intermittently with intervals when it is absent.

In the *first* case we may conclude that the disease known as diabetes mellitus, glycosuria, is present. There are then usually other symptoms present which serve to assist us in making the diagnosis and prognosis: a very large quantity of urine of high specific gravity, great thirst, emaciation, dryness of the skin, etc. This is not the place to enter into a detailed description of the nature, cause, progress, and complications of diabetes mellitus, and I may remark here, that in all such cases the physician is justified in making, if not an unfavorable, at least a very doubtful prognosis.

The prognosis is frequently more favorable in those cases in which the evacuation of a saccharine urine has been observed after injuries of the brain, similar to those which are caused by the so-called sugar-puncture in animals, provided, naturally, that the injury to the brain does not of itself demand a bad prognosis.

The *second* case, in which the urine contains only traces of

sugar, or, only occasionally, large amounts of it, is observed in the course of several different diseases, and even in perfectly healthy persons. The cause of it has hitherto been attributed to various conditions by different physiologists: to an immoderate use of saccharine and amylaceous substances, to disturbances of the functions of the brain and nervous system, especially of the medulla oblongata, to diminution of the respiration and absorption of oxygen, to excessive production of sugar by the liver, and to a diminution of the alkalies in the blood. It is always advisable for the physician in such a case to direct his attention to these etiological conditions and to ascertain whether any one of them is present, and to govern his therapeutics accordingly. But a perfectly satisfactory explanation and treatment of such a case will only be possible in the future, when the causes mentioned, which are still partly under discussion, shall be more accurately determined and their influence on the elimination of sugar with the urine shall be more perfectly known than is the case at present. In the meantime the following seems to be the most probable view: When from any cause a greater quantity of sugar accumulates in the blood than can be decomposed in it by the process of metamorphosis—whether it be that an unusual quantity of sugar gains access to the blood, or that its decomposition in the blood is hindered in any way—a part of the excess may be passed off with the urine, just as is the case with many other substances.

Under this head belongs the presence of small quantities of sugar in the blood of the arteries, veins, portal vein, in the urine of pregnant, lying-in, and nursing women, and also in the urine of perfectly healthy men. After much controversy in this matter it now appears tolerably certain from the investigations of Brücke and Iwanoff, and contrary to the assertion of Seegen (see page 101), that the urine of healthy persons even sometimes contains small quantities of sugar. Such investigations, however, have little value for the practitioner from a diagnostic point of view; they rather concern the chemist and physiologist. It is still very difficult to obtain reliable results in this matter, since in investigations of this sort only the most exact methods of procedure and the purest reagents will enable us to exclude errors. Then, too, no one should experiment in this direction without a perfect mastery of the literature of the

subject, which has already become quite extensive. The two comprehensive treatises of Lehmann,\* and the dissertation of Nicol. Iwanoff,† which contains the latest literature of the subject, will best serve to give a general idea of the matter.

According to De Sinety‡ sugar occurs in the urine of pregnant women and in lying-in women only when the lacteal glands are imperfectly emptied, when it regularly occurs. Consequently sugar is always found in the urine on the second or third day after delivery at the time of the milk fever. The secretion of milk at this time is quite abundant, while the child gets but little of it. The urine may be rendered saccharine at will in nursing dogs and rabbits by removing the young. The increase of sugar in the blood could be detected when the milk was not removed.

Sugar has sometimes been observed in the urine after having taken oil of turpentine (see page 102), also temporarily in tetanus rheumaticus§ and in persons suffering from intermittent fever.||

According to the investigations of L. Senff,¶ the urine of animals temporarily (two or three hours) contains sugar after they have been made to inhale carbonic oxide.

Ewald\*\* brought on glycosuria in rabbits and dogs by injecting nitrobenzol.

Külz †† also succeeded in producing glycosuria in dogs and rabbits by injecting various substances.

Inosite (compare § 27) has been found in the urine repeatedly of late, but always only in pathological cases, sometimes accompanied by grape sugar, sometimes with albumen in nephritis albuminosa. Its source and importance are still unknown.

\* Schmidt's Jahrb., Band 87, p. 281, and Band 97, p. 3, *et seq.*

† Beiträge zu der Frage über die Glycosurie der Schwangeren, Wöchnerinnen und Säugenden, Dorpat, 1861.

‡ Recherches sur l'urine pendant la lactation, Gaz. med. de Paris, 1873, No. 43 and 45.

§ A. Vogel, Deutsches Archiv f. klin. Med., 1872, x., p. 103.

| E. Burdel, De la Glycosurie éphémère dans les fièvres palustres, Union méd., 1872, Nro. 105, p. 368, *et seq.*

¶ Inaugural-dissert., Dorpat, 1869.

\*\* Centralblatt f. d. med. Wissensch., 1873, Nro. 52.

†† Beiträge zur Hydrurie und Melliturie, Habilitationsschrift, Marburg, 1872.

It appears, however, to come from the glycogen of the liver, for in puncture of the fourth ventricle of the brain in animals or in a corresponding organic disease of the brain inosuria is sometimes produced instead of glycosuria.

Cases of inosuria are described by Gallois,\* Schultzen,† and others.

Inosite was also detected in the urine in a case of polyuria with softening of the medulla described by Mosler.‡

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A few other substances which have been found in the urine in isolated cases, such as lactic acid (see § 30), various volatile fatty acids (see § 31), benzoic acid (§ 32), which occurs only in decomposing urine, sulphuretted hydrogen (§ 34), allantoin (§ 35), have at present so little practical significance that a discussion of them here is unnecessary. We shall speak of certain substances later, as leucin, tyrosin, etc., when they occur under circumstances which are of interest to the practitioner. (§ 112 and § 133.)

#### § 105. ACCIDENTAL ABNORMAL CONSTITUENTS.

Under this head are comprised various unusual constituents of the urine which are derived from the food, drink, medicines, etc., and which pass into the urine either changed or unchanged, thus rendering it abnormal, but without the abnormality having a pathological significance.

We have already in different places spoken of these accidental constituents of urine, their detection and signification. (§ 56, p. 190, etc.) They are of more special interest to the chemist and physiologist: to the former, because they acquaint him with many products of the decomposition of complex organic substances; and to the latter, in explaining changes which different substances undergo in the human and animal economy, and thus throw light on many points concerning the intermediate metamorphosis of tissue.

Among these substances which occasionally appear in the urine, and which are, at present at least, of more interest to

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\* De l'Inosurie, Paris, 1864.

† Arch. f. Anat., 1863, i., p. 23, *et seq.*

‡ Virchow's Archiv, 1873, lvi., p. 44, *et seq.*



chemists and physiologists than to practitioners, are to be considered small quantities of nitrates and nitrites (see § 21), which doubtless come from the food and drink consumed, and also small quantities of peroxide of hydrogen (see § 22). Both were first detected by Schönbein.\*

But they have also some importance for the physician, and in time will assume a still greater one. From their presence we may learn that a patient has taken certain food, drink, or medicine. Thus asparagus, oil of turpentine, saffron, cubebs, etc., betray themselves by the odor which they impart to the urine; many vegetable substances, as rhubarb, senna, certain roots and fruits containing pigment, sometimes also creosote, tar, and santonin (see page 368), when taken internally, betray their presence by coloring the urine; while other substances which pass into the urine may be detected by a chemical examination.

It is still more important to the physician to know whether certain medicines are eliminated with the urine, and if so, in what quantity, since the answer to this question frequently determines whether a patient shall continue the use of such remedies or omit them. (See page 358).

In many cases of poisoning, also, the poison may be detected in the urine, and the examination of the latter may be of importance at times in forensic medicine as well as in reference to diagnosis and treatment.

The following bodies are those whose detection in the urine is of especial interest to the physician:

The methods of detecting their presence are often quite complicated, therefore an accurate description here would take up too much space.†

*Lead* sometimes passes into the urine after lead poisoning and after the therapeutical use of preparations of lead. Its detection, however, is difficult and is not always successful.‡

*Copper* may generally be found in the urine after poisoning by copper. (Kletzinsky.)

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\* Journ. f. prakt. Chemie, 1864, p. 152, *et seq.*, and p. 168, *et seq.*

† See § 56, and the thorough treatise of Kletzinsky, Wiener medicin, Wochenschr., 1857 and 1858. Also Mayençon and Bergeret, Journ. de l'anat. et de physiol., 1872, Nro. 80-98; 1873, Nro. 8.

‡ See also Folwarczny, Wiener Zeitschrift, N. f., ii., b. 1859.



It may be of interest to the physician to detect the presence of mercury in the urine in mercurial poisoning and after mercurial treatment. In the latter case we may wish to know whether the mercury still exists in the economy, or whether it has already been eliminated. For the methods of proving this see page 192.

*Salts of zinc* pass readily into the urine, and may be detected in it without difficulty. (Kletzinsky.)

*Nickel* and *cobalt*, both of which, especially the former, have a poisonous action, may be recognized in the urine.

*Arsenic* and *antimony* also pass into the urine, and may be detected in it by the familiar processes by means of Marsh's apparatus.

The detection of iodine in the urine, after its exhibition, may sometimes interest the physician by indicating to him whether the economy still contains iodine or not. The amount of iodine in the urine may be very accurately determined quantitatively. (See page 197, and § 71.) The same is true of bromine. (See page 197.)

After the internal administration of the carbonates of the alkalis or vegetable alkaline salts (acetates, etc.) given as diuretics or to neutralize an excess of acid in the urine, it is often important for the physician to have a means which will enable him to determine how long such remedies may be given without injury, and when they shall be omitted, and when continued. In such cases the chemical reaction of the urine forms the best indication. As long as the urine has an acid reaction such remedies may be continued without injury, the system is not yet saturated with them.

If, however, the urine has a distinctly alkaline reaction, not from the presence of carbonate of ammonium, but from an excess of fixed alkalies (see page 377, b), it is best in most cases to omit the remedy, and to allow it to be repeated only after the urine has become acid again. The exhibition of these remedies should occur during the time when the stomach is empty, because during the two or four hours which follow a meal the urine is less acid, and sometimes even alkaline. (See § 127.)

*Tannic acid* passes into the urine as gallic or pyrogallie acid.

*Alcohol*, *carbolic acid*, and *chloroform* appear in the urine, and

may be detected in it according to the methods mentioned in § 56.

The greater part of *quinine* which has been absorbed, appears relatively soon in the urine again. By far the greatest part is eliminated in the first twelve hours after its exhibition in healthy persons, and in those suffering from fever; but in the latter, the chief part of the elimination takes place during the second six hours.\* For the process of detecting quinine in the urine, see page 204.

#### IV. URINARY SEDIMENTS.

##### § 106.

By urinary sediments is meant the occurrence of solid substances insoluble in the urine, which, at first, are usually suspended in it, and after a longer or shorter time sink and form a sediment. The deposit forms more rapidly and completely the coarser and heavier the solid particles in suspension are, and more slowly and incompletely the finer and lighter they are.

Slight sediments, consisting of very small molecules, which subside only with difficulty, and on shaking are very readily dispersed again, are only recognizable by a cloudy appearance and diminished transparency of the urine, and are called *turbidities* (clouds—*nubeculæ*). Sediments which consist of large particles distinctly visible to the unaided eye, like small grains of sand, are called *urinary sand* or *gravel*.

Urinary sediments give important information to the physician, and frequently enable him to recognize at once certain changes of the urine, which would otherwise often require a very tedious chemical investigation. Sometimes, indeed, a chemical test is necessary to determine the nature of a sediment, still more frequently a microscopic examination is required, and urinary sediments are among the objects for the accurate diagnosis of which a conscientious physician frequently requires the microscope.

The semiotic importance of urinary sediments is, like that of the urine, a double one.

1. They give information concerning certain changes in the

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\* H. Thau, *Deutsches Archiv f. klin. Med.*, v., p. 505, *et seq.*

*general metamorphosis of tissue* in disease. They teach the physician that an unusually large quantity of certain substances is separated with the urine, and, therefore, must be produced in the system; as, for example, hippuric acid, oxalic acid, etc. By their aid we are often able at a glance to learn much, frequently with absolute certainty, sometimes indeed only with probability, which is of value to the practitioner, and which the chemist in determining must attain by troublesome investigations.

2. They indicate to us certain *local* diseases of the uropoëtic system. Thus, the presence of a purulent sediment indicates suppuration in some part of the urinary apparatus; urinary casts indicate certain morbid changes in the parenchyma of the kidney; the chemical composition of gravel points out the probable composition of urinary calculi whose presence has been recognized by other means.

Some urinary sediments form before, and some after the urine has been passed; the former may give rise to urinary calculi under favorable circumstances, whereas the latter naturally cannot. For this reason, in many cases it is of practical importance to determine whether a sediment already existed in the urine when it was passed, or whether it formed in it afterward.

After these general considerations concerning urinary sediments, we will turn our attention to the importance of the individual constituents.

#### A. Non-Organized Sediments.

##### SEDIMENTS OF URIC ACID AND URATES.

##### § 107.

Sediments consisting of uric acid and urates occur very frequently in the urine; especially in *acute* febrile diseases, this variety of sediment occurs much more frequently than all of the other sediments taken together.

For their detection, see § 43 and § 44.

The conditions of their formation are, as a rule, complicated, and it is often difficult in any given case to determine how far one or the other of the causes mentioned below is active.

Uric acid is one of the normal constituents of urine, but it is soluble in it only with difficulty, and in small amount. When, therefore, changes in the urine occur which bring about such a condition that all of the uric acid contained in it cannot be retained in solution, the portion not dissolved is separated as a sediment.

These changes of the urine, which accompany the formation of uric acid sediments, may be divided into two groups, whose differentiation is of great practical importance :

1. The quantity of uric acid which passes into the urine in a given time (one hour, twenty-four hours) is greater than usual.

2. But if the urine secreted contains less water than usual, or in other words is very scanty, a uric acid sediment may be formed without the absolute secretion of uric acid being greater than usual.

A uric acid sediment in the urine, therefore, is not, as many physicians appear to believe, proof that there is an absolute increase in the quantity of uric acid formed and secreted. Such a conclusion is only justifiable when we have ascertained, according to § 73, and quantitatively determined the amount of uric acid passed within a given time (a known number of hours), and have found that it is greater than normal.

The causes which give rise to the formation of uric acid sediments are usually the following :

1. The urates are much more soluble in hot water than in cold. Consequently urine which is nearly saturated with these salts at the temperature of the human body throws down a sediment of urates on cooling. We frequently see, therefore, urine, which is perfectly clear on being passed, become cloudy from a separation of the urates, when it has lost the temperature of the body and become cool.

It is evident that urate sediments cannot easily occur in this way within the body during life, because the urine can never, except in the very rarest cases, undergo the necessary degree of cooling within the body. But it may happen that urine saturated with urates may undergo a further concentration in the urinary passages by endosmosis, so that a portion of its urates are rendered insoluble and precipitate, and thus form a sediment in the urinary passages ; such a case, however, appears to occur but very rarely.

2. The normal urates are more soluble than the acid salts, and the acid salts are more soluble than free uric acid. Consequently a sediment is formed whenever the normal salts in the urine containing them in large quantity are from any cause converted into acid salts or free uric acid.

We see this change occur out of the body during the acid fermentation. Uric acid sediments may be formed within the body for the same reason by either an acid fermentation of the urine, or a mutual decomposition of the urates and the acid phosphate of sodium, as has been already described in § 42, or when a very acid urine by a change in the secretion is mixed with the urine already in the bladder which is but slightly acid or even alkaline, in which case the acid urine abstracts the base from the normal urates either wholly or in part.

It is probable that the fermentation of the urine may also occasion uric acid sediments in other ways than by the formation of acid. The urinary pigments, indeed, appear to aid materially in the solution of uric acid in the urine. Consequently if the urinary pigment is partially altered and decomposed by the fermentation, a portion of the urates will be precipitated from the urine.

So much for the theory of the formation of these sediments: we will now turn to their practical importance.

Sediments of urates most frequently occur in acute febrile diseases or in febrile exacerbations of chronic diseases. In such cases almost always several of the above-mentioned predisposing causes act at the same time: diminution of the watery part of the urine, and consequently of the whole amount of urine, absolute increase of the uric acid, strongly acid urine, and a large amount of pigmentary matter in it. The sediment in such cases usually appears some little time after the urine has been passed, and its occurrence is caused partly by the cooling of the urine and partly by the commencement of urinary fermentation and decomposition of the pigment matters, in which such febrile urines usually abound.

The appearance of such sediments varies very much; sometimes they are of a clay color, sometimes brick red, rose or cinnamon colored—under the microscope they usually appear finely granular. They usually consist of normal or acid urates

whose base is sodium, potassium, or ammonium, more rarely calcium. (For their separation, see § 44.)

Their simplest diagnostic mark is, that the turbid urine containing them becomes clear on being heated and the turbidity returns on cooling.

Their importance consists in indicating that certain changes of metamorphosis occur in most febrile diseases (increased formation of uric acid and of pigment, together with diminished secretion of water with the urine). They are frequently regarded as critical. There is reason in this, in so far as the separation of an excess of uric acid from the blood may be a favorable sign, while a retention of it in the blood would produce evil consequences. They have, however, very often decidedly no critical significance, for we frequently see that the chief symptoms of the disease continue unabated for a long time after their appearance.

Sometimes such sediments appear in perfectly healthy persons when the above-mentioned conditions are present: they occur, for example, after violent bodily exercise, excessive eating, profuse perspiration with consequent diminution in the amount of urine; also after a night of revelry or a fatiguing excursion on foot in the heat of summer.

Since such sediments are almost always formed outside of the body, they only exceptionally give rise to the formation of urinary concretions.

It is of no practical importance to determine the *base* with which the uric acid is combined in such sediments, that is, whether the sediment consists of urate of sodium, potassium, ammonium, or calcium.

The urine more rarely contains sediments of *uric acid*. These usually occur in large crystals, often apparent to the unaided eye, or in the form of crystalline masses, sometimes alone, sometimes imbedded in a sediment of urates. Such sediments may arise when the urine becomes acid from one of the above-mentioned causes; and every sediment of urates may be artificially converted into a crystalline sediment of uric acid by the addition of an acid.

In this case it is important to ascertain whether the sediment has formed after the urine has been passed, or whether it already existed in the urinary passages, the kidneys, or bladder.

The latter is quite important, practically, because by its long continuance we have reason to fear that uric acid calculi may be formed in the kidneys or bladder of such a patient.

### § 108. HIPPURIC ACID.\*

We consider hippuric acid under the head of sediments, because it usually appears as a sediment in those cases which interest the physician, and because in this form it is more easily and quickly recognized by means of the microscope than chemically by evaporating the urine, etc. (See § 8.)

Sediments of hippuric acid are relatively rare; under the microscope they usually appear as rhombic prisms, and sometimes in the form of needles. (Plate I., fig. 1.) They may be confounded with uric acid crystals or crystals of ammonio-magnesian phosphate. They may be easily distinguished from the latter by their insolubility in hydrochloric acid; and from the former by not giving the murexide reaction characteristic of uric acid. Sometimes a sediment consists of a mixture of uric acid and hippuric acid crystals, and I have occasionally seen needle-shaped crystals of hippuric acid attached like spears to large crystals of uric acid. In cases of this kind it is best to collect the sediment on a filter and then to boil it in alcohol. This dissolves the hippuric acid only and leaves the uric acid undissolved. By evaporating the alcoholic solution we obtain the hippuric acid isolated, in the form of crystals, which may be more carefully tested and determined in the manner described in § 8.

An adequate number of investigations as to the amount of hippuric acid in normal urine, and its variations is not yet at our command. According to those which have been published thus far, the average quantity of hippuric acid in the urine

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\* W. Duchek, *Das Vorkommen der Hippursäure im Harn des Menschen*, Prager Vierteljahrschr., 1854, Band 8, p. 25, *et seq.* W. Hallwachs, *Ueber den Ursprung der Hippursäure im Harne der Pflanzenfresser*, Ann. d. Chem. und Pharm., 1858, Band 105, p. 207, *et seq.* R. Wreden, *Quantitative Bestimmung der Hippursäure mittelst des Titirverfahrens*, Journ. f. prakt. Chemie, 1859, Band 77, p. 446. A. Lücke, *Ueber die Anwesenheit der Hippursäure im menschlichen Harn und ihre Auffindung*, Virchow's Archiv, 1860, Band 19, p. 196. J. L. W. Thudichum, *Researches on the physiolog. variations of the quantity of hippuric acid in human urine*, Journ. of the Chem. Society. †



passed in twenty-four hours, by persons in health, amounts to from 0.17 to 1 grm., but after eating largely of those substances mentioned below, it rises much higher (to over 2 grm.). For further particulars see pages 47, 48.

According to Lawson the urine of the inhabitants of tropical countries, at least in Jamaica, is unusually abundant in hippuric acid.

The causes which determine the separation of hippuric acid as a sediment are quite the same as those mentioned under uric acid.

*Importance.* Large deposits of hippuric acid occur in the urine of persons in perfect health after they have eaten largely of fruit, and particularly prunes (Duchek), bilberries (*Vaccinium vitis idæa*), and mulberries (*Rubus chamaemorus*) (Lücke); also after taking benzoic and cinnamic acids, which are converted into hippuric acid in the body, and as such separated from the urine.

The statement of Kühne, that after the ingestion of succinic acid a large quantity of hippuric acid appears in the urine, could not be confirmed by Hallwachs, Lücke, and Meissner.

When the physician finds a large amount of hippuric acid in the urine of sick people, he must first of all ascertain whether it depends on any such cause (as the ingestion of fruit or benzoic acid). Yet, without doubt, a large amount of hippuric acid may be found in the urine, caused by morbid changes of the metamorphosis. Thus, hippuric acid has been found in large quantities in the acid urine of fevers, in which, indeed, it has been the chief source of the acid reaction (Lehmann); it has also been found in diabetes, chorea, etc. The observations, however, hitherto made concerning the presence of hippuric acid in the urine of the sick, are still very imperfect, and furnish nothing of value for the diagnosis, prognosis, and treatment of such cases.

The opinion that a tendency to the excessive formation of uric acid may be removed by the use of benzoic acid, in consequence of the uric acid in such a case being replaced by hippuric acid (Ure, Keller), has been proved to be erroneous, and at the same time the proposed administration of benzoic acid as a remedy in the uric acid diathesis is seen to be of no practical value.

During the last few years a large number of investigations



have been carried on with respect to the sources of hippuric acid in the urine both of human beings and of herbivorous animals, by which it is much more plentifully excreted.\* But they have thus far yielded no results which could be practically utilized by the physician. Yet it seems probable that the biliary acids, and consequently the liver indirectly, by their formation in the body play some part.†

### § 109. EARTHY PHOSPHATES.

(Phosphate of Calcium and Ammonio-magnesian Phosphate [Triple Phosphate].)

Earthy phosphates very frequently occur in urinary sediments and chiefly in chronic diseases and in alkaline urine, the reverse of the case with uric acid sediments. When the urine is alkaline they are never absent, whether the alkalinity is spontaneous or has been occasioned artificially by supersaturation of the free acid of the urine with caustic alkali or alkaline carbonate.

Its mode of origin is thus explained: When urine is rendered alkaline by the formation of carbonate of ammonium resulting from the decomposition of urea (compare § 96 and page 161), not only is its phosphate of calcium precipitated, being soluble only in acid fluids and not in alkaline ones, but it also forms by the action of the ammonia on the phosphate of magnesium always present in the urine, a triple phosphate of ammonio-magnesian phosphate, which separates, since it is insoluble in alkaline fluids. Since now all urine, with very rare exceptions, contains both phosphate of calcium and phosphate of magnesium, the alkaline fermentation produces a sediment in every urine consisting of a mixture of both of these earthy phosphates.

This sediment, according to Neubauer's numerous investigations,‡ contains on the average 67 parts of phosphate of magne-

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\* Besides the above literature, see especially E. Lautemann, *Ann. d. Chemie und Pharm.*, 1863, p. 9, *et seq.*, and Meissner and Shepard, *Untersuchungen über das Entstehen der Hippursäure*, Hannover, 1866.

† See Baumstark, *Berliner klin. Wochenschr.*, 1873, Nro. 4.

‡ *Journ. f. prakt. Chem.*, Band 57, p. 65, *et seq.*

sium and 33 parts of phosphate of calcium in 100 parts. (Compare also § 132.)

See § 46 for an account of the chemical and microscopic characters of this sediment. The triple phosphate is always distinctly crystalline, and its crystals are usually very well formed and shaped like a coffin lid (Plate II., fig. 3, 5, and 6); more rarely (only when it is freshly precipitated) it is less perfect, but even then its groups of crystals are none the less characteristic and closely resemble two fern leaves crossing each other at an acute angle.

Phosphate of calcium, on the other hand, usually appears amorphous under the microscope, in ill-defined, highly transparent flakes or cell-like spheres, only occasionally crystalline. (See page 169.) Frequently they are so transparent and their contour so badly defined, that some little practice is required to recognize them under the microscope. This is the reason why such sediments when examined microscopically so frequently appear to consist of triple phosphate alone, while, as a rule, one-third at least consists of phosphate of calcium.

The case is different when the alkaline condition of the urine does not depend on carbonate of ammonium, but on carbonate of potassium, sodium, or some other *fixed* alkali. Then no triple phosphate can form, and the sediment appears to consist only of phosphate of calcium.

Sometimes, however, crystalline deposits of phosphate of calcium without triple phosphate are formed even in faintly *acid* urine.\*

A. Riesell found a sediment of phosphate of calcium in the urine, which had already formed within the urinary passages, after the long-continued administration of chalk.

*Importance.* It was formerly the idea that sediments of the earthy phosphates were usually associated with an excess of these substances in the urine, and such cases were considered as so-called phosphatic diathesis. This is wholly erroneous: for *every* urine which is alkaline, and especially if it is ammoniacal, contains a sediment of the earthy phosphates, so that a sediment of this kind does not by any means indicate an abnor-

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\* Hassall, On the frequent occurrence of phosphate of calcium in the crystalline form in human urine, and on its pathological importance. Proceedings of the Royal Soc., x., 38, 1860, p. 281.

mally increased amount of earthy phosphates in the urine. An increase of the earthy phosphates can only be proved by a quantitative determination of their amount. (See § 76.) At most we can only give an approximate idea of the amount of earthy phosphates in a specimen of urine from the quantity of the sediment; according to § 91, however, this last process requires much practice and is not very trustworthy.

Independently of this approximate determination of the amount of earthy phosphates these sediments have a practical importance.

1. They are usually the first to indicate, to the physician that there is an alkaline condition of the urine with its consequences, and to prompt him to investigate its cause more carefully. (See § 96, especially page 377.)

2. In those cases in which the freshly passed urine already contains a sediment of earthy phosphates, it is evident that they must have been formed within the urinary passages, and consequently we may have reason to fear that they may give rise to the formation of phosphatic calculi, if this condition lasts a long time.

#### § 110. OXALATE OF LIME. CALCIC OXALATE.\*

Calcic oxalate is of especial importance to the physician as a urinary sediment, because in this form it is much more easily and quickly recognized by the aid of the microscope than by chemical analysis. We shall, therefore, consider here all of the different circumstances which have a bearing on the occurrence of this substance in the urine.

To recognize a sediment of calcic oxalate quickly in the urine, it is best to use tolerably high powers of the micro-

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\* F. W. Beneke, *Zur Physiologie und Pathologie des phosphorsauren und oxalsauren Kalkes*, Göttingen, 1850. Ibid., *Zur Entwicklungsgeschichte der Oxalurie*, Göttingen, 1852. James Begbie, *On Stomach and Nervous Disorders as connected with the Oxalic Diathesis*, *Edinburgh Monthly Journal of Med. Science*, August, 1849. Ch. Frick, in Baltimore, *Remarques sur la diathèse d'oxalate de chaux et sur son traitement*, *Gazette des hôpitaux*, 27 Septembre, 1849. Gallois, *Mem. sur l'oxalate de chaux dans les sédiments de l'urine, dans la gravelle et les calculs*, *Gaz. méd. de Paris*, 1859, Nro. 35, *et seq.* Smoler, *Studien über Oxalurie*, *Prager Vierteljahrschrift*, 1861. M. Seligsohn, *Centralbl. f. d. medic. Wissensch.*, 1873, No. 22, 27, 28, 33.

scope. The sediment is always crystalline, to be sure, but the crystals, as a rule, are very small, usually much smaller than blood or pus corpuscles. The form of the perfect crystal is always that of an envelope (quadrilateral-octahedron, Plate I, fig. 3). The smallest, even under high powers, always appear only as angular points, and on account of this minuteness of the crystals it is usually impossible to recognize a urinary sediment of calcic oxalate with the unaided eye. It is best when we suspect such a sediment to filter the urine, and to carefully scrape the precipitate from the filter while it is still moist. When it is placed under the microscope the practised eye will immediately recognize the crystals of calcic oxalate, as a rule mixed with epithelium, mucus, and fragments of fibres of the filter, and sometimes with other crystalline sediments, as for example uric acid. If the diagnosis is doubtful, the other tests for calcic oxalate given in § 45 will confirm it.

By this method we can discover the slightest traces of calcic oxalate in the urine, and we cannot be more certain by chemical means. Still, calcic oxalate may occur in solution in urine which contains no trace of sediment. (See page 165.)

*Causes and Importance.* The causes of the occurrence of calcic oxalate in the urine may be sought in the following facts:

1. Oxalic acid and calcic oxalate form a constituent of many articles of diet in the vegetable kingdom (wood sorrel, common sorrel, the familiar fruit of the *Solanum lycopersicum*, known by the name of love apples), and of many medicinal agents. (Leaving out of account the occasional therapeutical use of oxalic acid and its salts, oxalates are contained in the root of rhubarb, gentian, saponaria, etc.) Oxalic acid gains entrance into the body in this way, and is separated again by the urine either wholly or in part as calcic oxalate.

2. Oxalic acid is frequently formed as a secondary product by the decomposition of animal, vegetable, or mineral substances. Thus it is formed by the oxidation of uric acid, kreatinin, leucin, etc.; by the imperfect oxidation of sugar, starch, and salts of the vegetable acids, whereby these, instead of being wholly transformed into carbonates, become in part oxalates which contain less oxygen. It is, moreover, probable that oxalates may be formed from carbonates and bicarbonates, when a part of their oxygen is removed from them by a process

of reduction. These facts in a measure explain why oxalic acid may be formed in the human system under favorable circumstances; thus after taking carbonated drinks (champagne, seltzer water), in disturbances of the respiration where the supply of oxygen is diminished, after eating sugar in excessive amount, etc., although the special conditions under which this formation takes place are still undiscovered.

According to O. Schultzen,\* human urine normally contains in twenty-four hours about 0.1 grm. of calcic oxalate. (According to Neubauer it is sometimes quite free from it; see page 168.) In a few cases of icterus, however, this amount increased fivefold.

The question has been repeatedly raised how it happens that calcic oxalate, which is nearly insoluble in water, can pass through the walls of the vessels in the kidney and get into the urine. Some investigations by Neubauer† and Modderman‡ give information on these points, and show that calcic oxalate is somewhat soluble in the acid phosphate of sodium, and also that chloride of sodium, sulphate of sodium, chloride of potassium, etc., and even urea aid in its solution, though in slight degree.

What importance, with reference to the diagnosis, prognosis, and treatment of disease does the presence of calcic oxalate in the urine afford?

In this relation we must distinguish two classes of cases:

1. If the urine for a long time continuously, weeks or even months, contains large quantities of calcic oxalate, there exists a so-called *oxaluria*, *oxalic acid diathesis*. This condition always demands the careful attention of the attending physician for two reasons.

a. Because of the danger, under such circumstances, of calcic oxalate calculi, so-called mulberry calculi, being formed in the kidneys or bladder.

b. And on account of the evil effects which oxalic acid may have on the system generally. It is known that oxalic acid taken internally in large amount exerts a poisonous action, not

\* Quantit. Bestimmung des oxals. Kalkes im Harn, Archiv f. Anat. und Physiol., 1868, p. 719, *et seq.*

† Archiv f. wissenschaft. Heilkunde, 1853, p. 1, *et seq.*

‡ Schmidt's Jahrb., Band 123, p. 145, *et seq.*

only locally on the portion of the intestine with which it comes in contact, but also generally on the heart and nervous system. From this circumstance it becomes probable, theoretically, that a large formation of oxalic acid within the body may also be productive of dangerous consequences. Many physicians, especially in England and America (Prout, Begbie, Frick, and others), have observed and described such cases of oxaluria.

As little attention has hitherto been paid to this form of oxaluria in Germany, it appears desirable to give here in outline the very clear description of this disease as given by Begbie.\* He says:

There is a numerous class of patients, mostly persons in the prime of life and belonging to the male sex, ordinarily of a sanguineous or melancholy temperament, unaccustomed to vigorous exertion, usually belonging to the higher classes of society and accustomed to indulgence in the luxuries of life, especially of the table. They suffer from indigestion, from its mildest to its severest forms. Often no apparent disease is present, but only the discomfort which imperfect digestion and defective assimilation bring about—a feeling of weight and pressure at the pit of the stomach, with flatulence and palpitation a few hours after meals. More serious symptoms, however, frequently appear, which are not confined to the digestive apparatus, but exert a very profound influence on the nervous system and threaten the mind of the patient. Such patients are usually capricious, sensitive, and irritable, or dull, despondent, and melancholic; they are frequently worried with a fear of some serious disease threatening them, as consumption or disease of the heart, and on this account are not rarely very deeply disturbed mentally. In milder cases we observe in these patients the anxious bearing and general appearance of one whose health is disturbed—the tongue is coated, the skin dry, and the pulse irritated; in inveterate cases, a dirty, dingy countenance, increasing emaciation, falling out of the hair, tendency to furuncles, carbuncles, psoriasis, and other cutaneous diseases; dull, deep-seated pains in the back and loins, hæmorrhage from the intestine and bladder, incontinence of urine, and impotency. The progress of this affection may be slow and varied: under

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\* Loc. cit.

the influence of proper diet and appropriate treatment, combined with pure country air, the disorder may be arrested, and, even by appropriate therapeutic treatment, entirely removed. If, however, it be neglected or badly treated, the affection will surely expose its victim to all of the dangers and sufferings of a calculus in the kidney or bladder, or to the still worse consequences of a malignant organic disease.

The source of this affection is to be sought in the accumulation of oxalic acid in the blood. This poison is separated from the blood by the kidneys, and its separation in the form of calcic oxalate gives us a means of recognizing the disease, and thus inducing a cure by tolerably simple and efficacious treatment.

According to Begbie, this treatment is as follows: Long continuance in a proper diet of meat, milk, mealy vegetables, with the exclusion of saccharine substances; warm clothing and lukewarm baths; as drugs, nitrate of potassium, hydrochloric acid in doses of twenty drops two or three times a day, or in the following formula: *R. Acidi muriatici dil., acidi nitrici dil., syrupi aurantii āā ʒss, aquæ ʒiss*, of which one teaspoonful is to be taken in a wineglassful of water before meals.

Beneke\* describes the injurious influence of oxalic acid on the body even more forcibly. He believes that the phosphate of calcium is dissolved by it and removed from the body. The deficiency of phosphate of calcium which is thus brought about results in a diminution of the organic process of cell-formation.

Distinct proof is as yet wanting, however, that the symptoms described above as belonging to the oxalic diathesis really do depend on an accumulation of oxalic acid in the blood, and the assumption of an oxalic acid diathesis is, therefore, declared by many, as Lehmann, Gallois, and Smoler, to be quite improper. If, however, we recollect that oxalic acid undoubtedly possesses a distinct poisonous influence on the body when given in large doses, and that every observant physician with much practice has had opportunity to observe cases which quite correspond to the description given by Begbie (I have met with several such myself), it would appear justifiable to advise practitioners not to neglect those cases in which large quantities of calcic oxalate

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\* Loc. cit.



appear for a long time continuously in the urine, and, moreover, to investigate carefully its causes (disturbances of the respiration with diminished absorption of oxygen, immoderate eating of sugar, disturbances of any other intermediate metamorphosis), and to carry out the treatment recommended above.

2. On the other hand, it is certain that all of the cases in which calcic oxalate is observed in the urine do not come under the category described. Where only traces of this salt are found in the urine, or when large quantities of it appear only temporarily, as is often observed in the course of certain acute and chronic diseases, the danger spoken of above is not to be feared. The physician here has the task of investigating the cause of this occurrence: whether, perhaps, food or medicine containing oxalic acid gives rise to it; or whether demonstrable changes in metamorphosis are the cause. In such cases the prognosis is not so bad, and we have only rarely to fear the bad results of oxalic acid described above. But it appears advisable here also, after we have obtained the causes of the abnormal condition, to combat it at once by proper treatment (especially substituting an animal diet for a largely vegetable one), and thereby obviate the possible evil consequences.

### § 111. CYSTIN.\*

The practical signification of cystin is of relatively small importance, since it seldom occurs in the urine. We only know at present that cystin sometimes gives rise to the formation of calculi. In such cases it always appears as a urinary sediment, and for this reason we mention it here, though cystin may also exist in solution in the urine.

Whether the formation of this substance in the body is in any way injurious by producing alterations of the intermediate metamorphosis is not yet determined. It is not probable, however, since, according to experience, cystin may be present in the urine for years without disturbing the health when a cystin calculus is not formed.

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\* A. Fabre, *De la cystine*, etc., Paris, 1859. Jul. Müller, *Archiv d. Pharmacie*, 1852, p. 228, *et seq.* Toel, *Annal. d. Chemie u. Pharmacie*, Band 96, p. 24, *et seq.* Bartels, *Virchow's Archiv*, 1868, p. 419, *et seq.*



For the *detection* of this body in the urine by chemical and microscopic examination, see § 47.

The *causes* which give rise to its formation in the body are still quite unknown. The large amount of sulphur which it contains (more than 26 per cent.) indicates its relation to taurin, and we are, therefore, led to presume that perhaps the liver plays a role in its formation.

Indeed, Scherer has found cystin in the liver, a proof that this substance, like urea, uric acid, etc., is not formed in the kidneys but elsewhere in the body, that it is taken up by the blood and separated again from it by the kidneys.

Marowky \* observed a case in which the presence of cystin in the urine was combined with almost complete chronic acholia, and supposes that a vicarious elimination of the taurin, which contains sulphur, took place by the kidneys in the form of cystin.

Future investigations, let us hope, will yield information as to the significance of the appearance of cystin in the urine, and the more intimate conditions of its formation.

It is an interesting fact that in the tolerably rare cases in which cystin has been found in urinary calculi and sediments, it has been present in a large proportion of the cases in *several* members of the same family.

Two cases which I had the opportunity of observing a short time ago, through the kindness of Dr. H. Harnier of Wildungen, confirm this. They were two brothers, young Hollanders, born in the East Indies, both of whom, otherwise well, suffered from cystinuria, which at times increased to the formation of gravel and small calculi.

## § 112. XANTHIN. HYPOXANTHIN. TYROSIN.†

*Xanthin* (see § 5 and § 49), formerly found only in very rare cases as a constituent of human calculi, afterward found in very small quantity in human urine, etc., has recently been observed also as a crystalline urinary sediment.‡ The significance of such

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\* Deutsches Archiv f. klin. Med., iv., p. 449, *et seq.*

† Strecker, Annal. d. Chemie u. Pharm., Band 102, p. 108. Städeler, Ibid., Band 111, p. 28. Scherer, Ibid., Band 112, p. 257. Jaillard, Calcul de xanthine, Alger. médic., 1873, Nr. 1, u. Centralbl. f. d. medic. Wissensch., 1873, No. 35.

‡ Bence Jones, Journ. of the Chem. Society, 1862, p. 68, *et seq.*

a sediment for the practitioner depends only on its liability to cause the formation of urinary calculi. The causes which give rise to an increased formation of xanthin in the body and to its existence as a sediment are as yet unknown.

*Hypoxanthin* (sarkin) is a body closely allied to xanthin; it occurs in small quantity in different organs of the human body (spleen, liver, pancreas), and probably, also, sometimes in the urine. (Strecker.) It must undoubtedly be regarded as a product of animal metamorphosis, and in its chemical constitution it is very closely allied to uric acid. (Compare page 33.) Still, we know so little concerning its origin and signification at present, that it seems sufficient to merely mention it here.

Mosler \* lays stress on the appearance of hypoxanthin in the urine as a characteristic symptom of splenic leukæmia. Sal-kowsky † was unable to confirm its occurrence, and the same may be said of E. Reichardt. ‡

*Tyrosin* (see § 37 and § 48), is a substance which results from the decomposition of the protein substances. It has been observed in different organs of the human body, usually associated with leucin, and in rare cases it occurs as a urinary sediment. When it appears in considerable quantity in the urine it indicates alterations of the metamorphosis (excessive decomposition of the protein substances), and thus is of interest to the physician. It has thus far been found in the urine, especially in acute atrophy of the liver, and is to a certain degree characteristic of this disease. It was also present in a few cases of leukæmia, typhoid fever, small-pox, etc. (Compare also § 133.)

## B. Organized Sediments.

### MUCUS AND EPITHELIUM.

#### § 113.

Urinary sediments consisting of mucus and epithelium are quite important to the practitioner, and as they usually appear together, we will consider them together here.

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\* Virchow's Archiv, 37, p. 43, *et seq.*

† Virchow's Archiv, 1870, 50, p. 174, *et seq.*

‡ Jena'sche Zeitschrift, v., p. 889, *et seq.*

All urine, even of healthy people, contains a little mucus, which is derived from the mucous membrane of the urinary passages, particularly of the bladder and urethra. In women, not unfrequently, mucus and epithelium from the vagina are mixed with the urine. The presence of a small amount of mucus in the urine, therefore, has no pathological importance. It usually appears in the form of a light cloud, which very gradually sinks to the bottom, and is best recognized when the urine is observed in a glass by transmitted light.

When there is an abnormal increase in the amount of mucus this cloud increases, and a slimy sediment appears when the urine is left at rest for a time. With a little practice we can determine approximately by observation the quantity of mucus, and, moreover, this method of its estimation not only accomplishes our object more quickly, but, as a rule, gives better results even than the very complicated chemical processes which are not easily employed by the physician.

For the *detection* of mucus see § 50. Pure mucus is recognized under the microscope only with difficulty or not at all, since it forms a perfectly transparent mass which does not catch the eye. Epithelial cells, found mixed with it, are very distinctly recognized, however, from their characteristic appearances. If the mucus is precipitated by alcohol, or acids, however, it is recognized very readily as an indistinctly fibrillated mass. It is rendered more distinct by the addition of diluted tincture of iodine, which not only precipitates, but colors it.

If such a specimen of urine is filtered, the mucus remains as a tenacious mass on the filter, and, after drying, has a varnish-like appearance. A small quantity of mucus may remain in solution in the urine even after filtering, and this gives the chemical characteristics of mucin, described on page 175.

The microscope shows us that the slimy urinary sediment frequently includes, in addition to the epithelium, other foreign matters: spermatozoa, crystals of calcic oxalate, urates, ammonio-magnesian phosphate, etc.; therefore, in all cases in which an accurate diagnosis is required, this supposed mucus must be carefully examined with the microscope.

An increased quantity of mucus in the urine indicates to the physician that there is an irritation of the mucous membrane

(blenorrhœa) in some part of the uropoëtic system—or in women, of the genital mucous membrane. This blenorrhœa may form a purely *local* process, or it may be the result of a *general* disease. For the latter reason the quantity of mucus and epithelium appears to be increased in the urine not unfrequently in various febrile diseases—typhoid fever, pneumonia, etc.

In a circumscribed blenorrhœa of the urinary passages, the situation of the affection may sometimes be recognized by the shape of the epithelial cells.

The desquamated epithelium of the *urinary tubules* almost always forms large cylindrical bodies having the diameter and shape of the urinary tubules (epithelial casts). (Compare § 116, 1.)

The epithelium of the rest of the urinary passages from the pelvis of the kidney to the urethra is of the pavement variety, arranged in several layers. The most superficial layer consists of more or less flat cells, which in the pelvis of the kidney appear on the whole smaller, less flattened, sometimes irregular and furnished with projections; while in the bladder they are usually larger and more flattened, and sometimes present grooved depressions on their posterior surface which is turned toward the middle layer. The middle layer consists especially of smaller, more oval and club-shaped caudate cells. The deepest layer of cells consists of still smaller round cells, so-called mucous corpuscles.

If we bear in mind these relations, we may frequently be enabled to determine whether the desquamated epithelium contained in the urine came from the urinary tubules or from a lower portion of the urinary passages; and, in the latter case, whether it belonged to the superficial or deep layers, and whether it came from the pelvis of the kidney or the bladder.

When there is a very great increase in the quantity of mucus in the urine, there is almost always a tendency to the acid or alkaline fermentation, which the practitioner must carefully take into consideration on account of the attendant results—increased irritation of the mucous membrane of the urinary passages and formation of urinary concretions.

Further, we may observe that pus corpuscles in ammoniacal urine may be converted into a jelly, which bears the greatest

resemblance to mucus, so that the physician frequently supposes he has a mucous urinary sediment before him, when in reality it does not consist of mucus, but of pus corpuscles which have been transformed into a gelatinous mass. (See the following section.)

#### § 114. Pus.

*Recognition.* The microscope is always required to distinguish pus in the urine with certainty. With it pus corpuscles are recognized by their shape and size, as well as by the very characteristic nuclei which are made clear by the addition of acetic acid. (See § 52.) The *abnormal* pus corpuscles described below form the only exception to this. A discrimination between pus corpuscles and so-called mucous corpuscles is neither possible nor of practical importance, since the two kinds of corpuscles are quite identical.

Large quantities of pus in the urine always form a sediment.

If only a few pus corpuscles are present in the urine, a visible sediment is a long while in forming. To discover the pus corpuscles in this case the urine must either be allowed to stand for several hours in a tall glass and then the lowest layer be examined microscopically, or we must filter it and place that which remains on the filter under the microscope for examination.

There are cases, however, in which pus cannot be detected in the urine with certainty, but can only be inferred. This happens when the urine containing the pus is strongly ammoniacal. The pus corpuscles are changed into a ropy gelatinous mass by the carbonate of ammonium present, and their shape and outline is destroyed. Such a mass is generally taken for mucus and the process causing it regarded as a blenorrhœa, when in fact it is a pyorrhœa, and the presumed mucus is merely pus, whose corpuscles have been destroyed by the influence of the alkali.

Since in every suppuration in addition to the pus corpuscles there is also present a pus serum which contains albumen, it is evident that all urine containing pus also contains a little albumen, which may be demonstrated by the usual tests; naturally when the urine is alkaline the necessary precautions must be taken. (Compare § 97.)

*Importance.* Pus in the urine always indicates a suppurative process in the uropoëtic system or an abscess communicating with it. Only in women is it possible that pus in the urine may be derived from the genital organs, the vagina, or the uterus.

Pus in the urine may be derived from the different parts of the uropoëtic system: from the urethra in gonorrhoea, from the bladder, the ureters, the pelves of the kidneys, and even from the parenchyma of the kidney in suppuration of that organ. It may spring from several of these parts of the uropoëtic system at the same time. The accurate determination of the true source of pus does not always appear to be easy. The following points, however, may prove of some service in the diagnosis:

In blenorrhoea of the urethra a purulent fluid may be pressed out of the urethra between the micturitions. The secretion then appears usually in the form of shreds in the urine.

If the pus come from the bladder symptoms of acute or chronic disease of the bladder are always present (strangury, etc.).

Suppuration in one or both ureters is accompanied by slight colicky pains along the course of the ureter.

Suppuration confined to the parenchyma of the kidney is sometimes accompanied by so slight local symptoms, that it is only discovered accidentally by the continued presence of pus in the urine.

*Example.* K., a man thirty-six years of age, entered the Giesen clinic on account of a rheumatic-gastric fever. He recovered rapidly, and was about to be discharged, when the sudden occurrence of a tolerably abundant sediment of pus corpuscles in his urine occasioned his retention in the hospital for a short time longer for observation. This sediment continued for weeks, the patient not having the slightest difficulty of micturition, indeed no symptom which pointed to disease of the uropoëtic system. Subsequently pain was felt in the region of one kidney and frequent chills occurred. An intercurrent typhoid fever, which was then epidemic, unexpectedly put an end to the patient's life, and the autopsy showed an almost complete suppuration of the parenchyma of one kidney without any further disease in the urinary apparatus.

It is of great practical importance in such cases to determine whether the pus is the product of a superficial affection of the mucous membrane (catarrhal inflammation), or whether it is the result of a more profound and extensive alteration of the parts. The following facts will assist in deciding this question :

The *duration* of the suppuration. The temporary presence of pus in the urine, lasting only a few days, always allows us to conclude that there is merely a superficial affection.

The *character* of the pus as seen on microscopic examination. Perfectly normal pus corpuscles of quite round shape presenting on treatment with acetic acid the characteristic double or triple nuclei indicate laudable pus and a simple catarrh of the mucous membrane. Abnormal pus corpuscles, on the other hand, with irregular forms and contours, and which present irregular nuclei on treating with acetic acid, or an ill-defined, finely granular mass mixed with irregularly shaped pus corpuscles and partially destroyed cells, indicate the probable existence of a deep-seated suppuration, ulceration, or tuberculosis. (Compare the following section.)

Various substances were formerly included under the head of pus in the widest sense of the word, which could not be distinguished by the unaided eye, and which the microscope alone has now allowed us to distinguish. The recognition of these substances has a great practical significance. Of this class are cancerous and tuberculous masses and urinary casts.

#### § 115. CANCEROUS AND TUBERCULOUS MASSES.

Cancerous and tuberculous masses sometimes occur as urinary sediment, and are important in indicating to the physician the fact that softening has occurred in cancerous or tuberculous deposits in some portion of the urinary organs.

Masses of cancer occur in the urine most frequently as the result of cancer of the bladder, more rarely of cancer of the kidney. The cancer is generally of the soft variety, encephaloid, and, as a rule, appears in the urine in the form of small masses, aggregations of cells—mother and daughter cells—with thick walls or caudate and long spindle-shaped cells. In such cases the urine also usually contains blood and blood coagula.

Distinct symptoms of disease of the bladder are always pres-



ent in cancer of that organ : difficulty of micturition, frequently also symptoms which point to a simultaneous disease of the rectum, or in women of the vagina, so that the diagnosis usually presents no difficulties.

Cancer of the bladder is generally a so-called villous cancer, that is, it is made up of compound branched villi, which are sometimes hollow and consist of a fibrous stroma covered with a layer of variously shaped epithelial cells ; sometimes also it consists of an amorphous base with cells imbedded in it. The detached portions of this cancer of the bladder, which occur as a sediment in the urine of those patients in whom the cancer has softened and separated, are, therefore, of very various shapes, but at the same time they are very characteristic and are of essential service in enabling us to diagnosticate such a disease with certainty.

Fig. 5 and 6 in Plate III. represent a few of the most characteristic forms of such cancers as they appear in the urinary sediment. They are in part taken from the valuable work of Dr. Lambl,\* and partly from my own observations. Fig. 5, A, represents a large fragment of villous cancer of the bladder, very branched, as it appears with a low magnifying power (from 20 to 50 diameters).

B represents the terminal portion of a villous cancer more highly magnified (about 200 diameters). The inner part consists of an amorphous fibrous stroma containing numerous oval nuclei and externally covered with a compound layer of epithelial cells.

C represents isolated cells from the epithelial layer of such a cancer. They are mostly irregular in form, partly caudate and branched, quite large, and containing a large nucleus.

D is a villous cancer of a somewhat different character. Tolerably large nuclei are enclosed in an amorphous mass which forms warty excrescences. The epithelial layer is wanting.

Fig. 6, A. Fragment of a villous cancer consisting of a fibrous (hollow?) cylinder, which is covered with epithelium (in the figure stripped off in places) in the form of small nucleated cells.

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\* Ueber Harnblasenkrebs. Ein Beitrag zur mikroskopischen Diagnostik am Krankenbette mit vier Tafeln. Prager Vierteljahrschr., 1856, Band 49, p. 1, *et seq.*



B is a mass of large cancer-cells with large cell-cavities, thick cell-wall and nuclei; the latter in some cases is enclosed in the cell-wall (B, c). The cells are partly united by means of an amorphous connective substance into large groups (B, a), and they are in part isolated (B, b, and B, c).

C. Fragment of an amorphous, fibrous cancer stroma having spindle-shaped nuclei and elastic fibres, on which larger cells rest—the remains of the epithelial covering—in part well preserved (aa), in part half destroyed (b).

D. Isolated cells probably derived from the epithelial covering of a villous cancer of the bladder; aa, small round cells with nucleoli (or nuclei?) distinctly colored red, and at first sight resembling blood corpuscles; in large masses forming a urinary sediment resembling blood, but not affected by acetic acid; bb, large, irregular, partly caudate cells, having reddish nuclei containing nucleoli. They are found mixed with the small cells (nuclei?), aa. (Compare § 134, case 13.)

Cancer of the kidney, on the other hand, is usually much more difficult to diagnosticate. Sometimes when cancer-cells are present in the urine, we can determine the existence of the disease by negative signs, as all symptoms pointing to a disease of the bladder are wanting; sometimes also we can determine it by percussion through an enlargement of one or both kidneys.

Masses of tubercle in the urine resemble pus when seen with the unaided eye, but they may be distinguished from it by their microscopic appearance. They consist of irregular pus corpuscles in addition to an ill-defined detritus—fragments of cells, necrosed connective tissue and elastic fibres, imperfect nuclei, and an indistinct, finely granular mass with which fragments of cholesterin crystals are sometimes mingled. The seat of the tubercular deposit which gives rise to urinary sediments of softened masses of tubercle is the mucous membrane or the submucous tissue; it may take place in the bladder, the ureters, or the calices of the kidney. In affections of this kind, which have lasted a long time, the tubercular deposit, as a rule, extends over a great portion of the mucous membrane of the urinary tract, from the kidneys even to the bladder.

The following histories of patients may serve to give information concerning the diagnosis of tubercular deposits in the uropoëtic system:

1. A young man, twenty-five years old, sought aid at my clinic for an affection of the bladder which had troubled him for a year. Micturition was difficult and painful, the urine was sometimes bloody, and deposited a sediment on standing, which contained blood and pus corpuscles partly normal and partly abnormal. (The latter were not perfectly round, but were angular and knobbed; when treated with acetic acid, they did not show normal nuclei, but were either wholly without nuclei or showed only small irregular nucleoli.) Besides this the sediment contained an irregular, granular, amorphous mass, in part finely divided, in part combined into larger masses up to the size of the head of a pin. A careful examination, moreover, showed that the prostate was enlarged, very sensitive on pressure, and that there was an advanced tuberculosis of the lungs. The patient had never suffered from gonorrhoea or chancre. A diagnosis of tuberculosis of the bladder and prostate was made, and on the death of the patient a short time after from increase of the lung trouble, the diagnosis was confirmed by the autopsy.

2. A man thirty years old, who had always been healthy, was seized with occasional attacks of pain, which passed from the region of the left kidney down to the bladder and terminated in very urgent and frequent calls to micturate. These paroxysms lasted several hours, and were repeated again after intervals of complete intermission which sometimes covered a few days only, and sometimes lasted for several weeks. Half a year later a swelling formed in the left testicle, this broke and led to the formation of a fistula which obstinately resisted all attempts to heal it. The urine never contained gravel or concretions, such as would lead to the suspicion of calculus of the kidney, but after every attack it deposited a slight sediment consisting of pus cells, which, as in the former case, were very irregular, and when treated with acetic acid presented no normal nuclei. Here, also, there was found in addition an ill-defined amorphous granular mass of the same appearance as that presented by tubercle-detritus under the microscope. This circumstance, together with the accompanying disease of the testicle, admitted of the diagnosis of tubercular deposit in the left ureter. \*

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\* Compare also Kussmaul, *Würzburger med. Zeitschr.*, 1863, p. 24, *et seq.*

## § 116. URINARY CYLINDERS. RENAL CASTS.\*

Urinary sediment, consisting of renal casts and cylinders, is of great practical importance in giving us information which will enable us to form a diagnosis and an opinion concerning certain diseases of the parenchyma of the kidney. This sediment can be recognized with certainty only by a microscopic examination. Its forms and characteristics have been already described in § 53; we must return to this subject again, however, in order to explain its importance under certain circumstances.

This sediment consists of long tubular or cylindrical bodies, which are formed in the urinary tubuli of the kidneys, especially the tubes of Bellini in the medullary portion, and which take the form of these tubules more or less, and to a certain extent form casts of them. The chief forms under which the elements of this sediment appear are as follows:

1. *Epithelial Casts*: Tubular masses of epithelial cells like those obtained by scraping with a knife a section of a fresh kidney through the medullary portion, and examining the fluid obtained microscopically. (See Plate I, fig. 4.) The epithelium of the tubules of Bellini is thrown off in coherent masses by a pathological process and is evacuated with the urine. Besides these larger epithelial tubules, single epithelial cylinders (ciliate cells) are frequently found which are derived from the calices or the pelvis of the kidney (Plate I, fig. 4); sometimes also pus corpuscles are present.

2. *Granular Renal Casts* (Plate I, fig. 6). These are solid cylinders, resembling those just described in form and size, but of a finely granular appearance. Sometimes they enclose single epithelial cells, more frequently blood corpuscles, pus corpuscles, as well as different kinds of crystals met with in urinary sediments, especially calcic oxalate. Blood corpuscles, pus corpuscles, or granule cells are very often found mixed with them in the sediment.

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\* L. Rovida, Ueber das Wesen der Harncylinder in Moleschott's Unters. zur Naturlehre, xl., p. 1, *et seq.* A. Burkart, Die Harncylinder, Gekrönte Preisschrift, Berlin, Hirschwald, 1874. H. Senator, Ueber die im Harne vorkommenden Eiweisskörper, etc., über Harncylinder und Fibrinausschwitzung, Virchow's Archiv, 1874, lx., p. 466, *et seq.*

3. *Hyaline Renal Casts* (Plate I., fig. 5). These are also solid cylinders, like the last, but they are so pale and transparent that it is very difficult to distinguish them under the microscope from the surrounding fluid. They are rendered more distinct by adding to the urine a little solution of iodine in iodide of potassium or in glycerine, which gives them a brownish color.

There are many transitions between the forms 2 and 3; the hyaline casts, for example, take up pus corpuscles here and there, or granular molecules or fat drops and fat granules, and thus resemble the granular form.

Moreover, we should observe the diameter of these casts. Sometimes the diameter is small,  $\frac{1}{10}$  of a line; in other cases it is larger and may reach  $\frac{1}{8}$  of a line or more. Sometimes the casts are of unequal diameter, they are small at one point and broader at another, varicose or flask-shaped.

Since casts and cylinders in many cases occur only in small numbers in the urine, to ascertain with certainty whether any are present or not, we must either allow the urine to stand a long time and examine the sediment microscopically, or what is still better, we must filter it and place the magma which remains on the filter under the microscope, as this will contain all of the casts and cylinders. It is a good plan to color the urine by adding a solution of iodine in iodide of potassium, so as not to overlook any of the transparent hyaline cylinders, which are so difficult to see. Sometimes forms are met with in the urinary sediment which somewhat resemble granular casts, and which may be erroneously mistaken for them. Such are cylindrical, sausage-shaped bodies which consist of masses of fine molecules. (Plate II., fig. 2.) They are found chiefly in albuminous urine, or in urine which has stood a long time and has already undergone partial decomposition. They result from a finely granular precipitation of albumen, mucus and the like. The skilled observer readily distinguishes them from true granular casts by their less regular shape.

*Importance.* Renal casts and cylinders always spring from the urinary tubules of the kidneys, especially from the tubules of Bellini in the medullary portion, and they indicate disease of these tubules. They are usually regarded as a sure sign of so-called Bright's disease. Since, however, the name "morbus Brightii" is at most only a somewhat indefinite collective term,

under which all varieties of disease of the renal parenchyma are usually included, it is insufficient for a careful diagnosis, prognosis, and treatment. We will attempt in the following pages to ascertain a little more accurately the indications of the different forms of these products.

*Epithelial casts* in the urine indicate that a separation of the epithelium of the tubules of Bellini (desquamative nephritis) is taking place. This process may be temporary without leaving any further consequences behind. Therefore a urinary sediment which consists merely of epithelial casts and which disappears again in a few days allows of a favorable prognosis. If pus corpuscles are found mingled with the epithelial casts, this points to a more severe inflammatory process (pyorrhœa) either in the parenchyma of the kidney or in the calices and pelves of the kidneys.

*Granular and hyaline casts*, on the other hand, always indicate a graver disease of the parenchyma of the kidney, which generally assumes a chronic course. The hyaline casts probably arise from an exudation of a fibrinous fluid into the renal canals with subsequent coagulation of the fibrine (croupous inflammation). The granular casts are formed either by a further metamorphosis of the exudation in the urinary tubules or by a degeneration of the glandular epithelium lining the tubules.

According to Rovida the colorless renal casts do not consist of fibrine and are also different from other kinds of albumen. Senator also does not consider the albuminous renal casts of all diffuse diseases of the kidneys as blood or exudation fibrine, but as products of the disturbance of nutrition of the glandular epithelium.

The larger the quantity of casts in the urine and the longer time they are present, the more extensive is the degeneration of the kidney apt to be, and as a rule, therefore, the more unfavorable is the prognosis.

If there is quite an amount of fat in the casts, and if it lasts a long time (recognizable as fat drops and granules imbedded in the casts), we may infer that the degeneration of the kidneys inclines to a fatty one.

When blood continues to be present in the casts, or in the urine containing casts, we may conclude that there is especially a disease of the vessels of the kidney—rigidity, fatty or amy-

loid degeneration of the renal arteries, especially of the vascular coils, which, as Malpighian bodies, project into the origins of the renal tubules.

Casts of very small diameter indicate a probable contraction and narrowing of the renal tubules, and unusually large ones indicate a dilatation of the renal tubules. Casts of very unequal diameter, with bulgings and contractions, allow of the conclusion that there is a varicose or distended condition of the renal tubules.

When, as often happens, several of the modifications mentioned occur together, we have reason to assume that the pathologico-anatomical changes in the kidney are very complicated.

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*Blood corpuscles* occur not infrequently as a urinary sediment. (Compare § 51 and § 99). We have already spoken of their significance to the physician in § 99. If they are in moderate quantity, together with renal casts and pus corpuscles, we may conclude that we are dealing with a case of a commencing or an advanced nephritis parenchymatosa or Bright's disease.

In rare cases granules or flakes of blackish-brown pigment are found in the urinary sediment. S. von Basch \* describes them as pale flocculi thickly filled with dark brownish, finely granular pigment, some of which have the shape and size of cells, while the most of them are much larger and are of irregular shape. They indicate a plugging and rupture of the renal vessels produced by the melanæmia.† (See page 394.)

#### § 117. INFUSORIA. FUNGI—(KYESTEINE).‡

*Fungi* and *infusoria* rarely exist in fresh normal urine; they must, therefore, gain access to it accidentally through unclean vessels, etc. They occur frequently, however, in urine which

\* A case of melanæmia. Wiener medic. Jahrb., 1873, ii.

† Further details may be found in J. Vogel's Krankheiten der harnbereitenden Organe, in R. Virchow's Handbuch der Pathologie und Therapie, Band vi., p. 600.

‡ A. Hill Hassall on the development and signification of *Vibrio lineola*, Bodo *urinarius*, and on other fungoid products, etc., in urine, Lancet, Nov. 1859, ii. 21.

has been kept a long time, and are almost always present in urine which has undergone decomposition.

L. Pasteur\* rightly calls attention to the fact that the germs of these fungi and infusoria always get into the urine from without, and are not formed in it by the so-called generatio *æquivoca*; moreover, it is usually after the urine has been passed that the fungi and infusoria appear, and they are the true cause of the acid and alkaline fermentations as well as of the decomposition of the urine. Urine from which these germs have been carefully excluded may be kept without decomposing. Since they are in any case the chief cause of a putrid decomposition of the urine with all of its results, such as decomposition of the urea, precipitation of many of the urinary constituents, irritation of the mucous membrane of the urinary passages, etc., we must take heed that such germs do not gain access to the urinary passages by the passage of unclean catheters, etc., and by rapidly increasing there bring about the evil consequences mentioned.

The *infusoria* are almost always very small, and are recognized under the microscope, when quite high powers are used, by their motion. They consist either of punctiform monads or of rod-like vibriones and bacteria. Rarely they are larger, roundish, resemble mucous cells and have thread-like appendages (Bodo urinarius—Hassall). They are found chiefly in putrid urine which contains albumen, mucus, blood, or pus, and are practically important, since they may favor or even set up putrid decomposition of such a specimen of urine. If they have formed already within the urinary passages, their germs have probably always obtained entrance from without, frequently in the manner described, by the introduction of unclean catheters. In all such cases, however, we must satisfy ourselves that the vibriones have not come from accidental mixture of putrid matters with the urine after its passage, from unclean vessels, or similar sources.

*Fungi* usually appear in the urine in the form of roundish or oval cells (spores and sporules), which are sometimes united in rows like a rosary (torula form)—less frequently they appear in the form of simple, compound or branched threads (thallus,

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\* Comptes rendus, 1860, i., p. 841.



mycelium). These latter usually do not occur until after the urine has been kept a long time, and, therefore, they are not of much practical importance. Of these fungi which occur in urine, those which are of chief interest to the physician are :

1. The torula-like fungus observed by Von Tieghem and described on page 188, on which the alkaline fermentation of urine is said to depend. The conditions of its origin and development, however, require a more accurate investigation.

2. *Yeast spores* (*Hormiscium sacchari*), which occur only in saccharine urines, and may, therefore, be utilized for the detection of glycosuria. They are also roundish or oval cells, which sometimes enclose a nucleus; they are, however, somewhat larger than the preceding (0.004 to 0.007 mm. in diameter). They increase by budding to torula-like rows, which are composed of from two to four cells. (See Plate II., fig. 2, and page 189, fig. 5.)

3. *Sarcinæ* (vide page 189, fig. 6). It appears to have quite as little real specific significance in the urine as it has in other cavities of the body (stomach and intestines, lungs), where it appears more frequently; it is probably, therefore, to be regarded as an accidental parasite. The presence of *sarcinæ* in the bladder probably favors the decomposition of the urine, produces alkalinity, a deposition of the earthy phosphates, etc., and therefore it has a practical interest.\*

Other fungi which are occasionally observed in urine which has been kept a long time belong to the most common forms, as *penicilium*, etc., whose spores are very widely disseminated, and may develop in the urine under favorable conditions when they have gained access to it. They are, therefore, without significance to the physician.

Under this head belongs the so-called *Kyesteine* which was thought to be present only in the urine of pregnant women; and therefore that it could be utilized as a means of diagnosing pregnancy. This name was applied to a pellicle which forms on the surface of urine after it had stood for a long time, usually several days. Microscopic examination of it shows, however, that it consists of very various elements, for the most

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\* Besides the literature already mentioned, see also *Sarcinæ in the Urine* (F. Bateman, *Lancet*, 1867, i., No. 6).



part of a large mass of vibriones with fungi, of crystals of ammonio-magnesian phosphate, small drops of fat, etc.; it is, therefore, no simple substance which requires a special name. Moreover, this pellicle does not occur exclusively in the urine of pregnant women, but is also found frequently in that of women not pregnant, and even in that of men, so that it has no diagnostic value for pregnancy.

### § 118. SPERMATOGA.

Spermatozoa can be detected in the urine only by the aid of quite high powers of the microscope. They are readily recognized by their peculiar tadpole shape. Since they rarely occur in large numbers, often only a single one being found in the urine, it is necessary to allow the urine to stand at rest in a conical glass (champagne glass) for a long time in order to find them with certainty; this is accomplished by carefully pouring off the upper part of the urine, and then examining microscopically the lowest part which contains the spermatozoa.

Their *importance* is self-evident. In the urine of men they always indicate that a discharge of semen has taken place either from coitus or masturbation; sometimes they lead to the detection of onanism. In the urine of women they prove that coitus has taken place, provided that there has been no admixture of semen, intentional or otherwise, with the urine.

The immature spermatozoa sometimes found by Clemens in the urine\* indicates to the physician that an unusually powerful or an immoderately long-continued irritation of the genital apparatus has occurred, whereby not only mature but also immature spermatozoa have been ejected (onanism, excessive coitus, etc.).

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In rare cases entozoa also occur as a urinary sediment, when they have gained access to the kidneys or some other part of the urinary passages, and are passed with the urine.

Of these the most frequent in Europe are: *Ecchinococcus cysts*, usually numerous, of the size of a pea, hazel-nut, walnut,

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\* Henle and Pfeuffer's Zeitschrift, 1846, v., p. 183, and Deutsche Klinik, 1860, 80. See also page 187.

and larger, formed of a structureless membrane and filled with serous fluid. Sometimes when these bladders are not sterile, the characteristic echinococcus heads and hooks may be seen with the microscope. Most of the echinococci which pass off with the urine are located in the kidney, though echinococci may also be situated elsewhere, in the pelvis, etc., make an opening into the urinary organs, and thus pass off with the urine.

The following example will show how difficult it may sometimes be to properly estimate such cases. A middle-aged man, otherwise well, suffered for years with a difficulty which occurred in paroxysms after longer or shorter intervals, and which indicated a disease of the urinary passages: there was occasional pain in the region of the left kidney, with albumen and pus, and sometimes also a moderate amount of blood in the urine. Various diagnoses were made by different physicians who were consulted, and corresponding courses of treatment were pursued (courses at Vichy, Karlsbad, etc.), but with no improvement; they, together with the ever-increasing fear that a serious renal disease existed which would shortly terminate fatally, rather reduced the patient. A careful examination of the urine passed during the attacks frequently showed the presence of small membranous shreds, which were recognized by the microscope as fragments of a sterile echinococcus bladder. Since percussion gave only a moderate enlargement of the left kidney and the natural passage of the echinococcus bladders had commenced in a relatively favorable way, a not unfavorable prognosis was given. The patient, freed from his anxiety and under treatment which, besides mild diuretics, had as its chief object the avoidance of matters which could be injurious, recovered in a comparatively short time.\*

In Egypt the eggs of the *Distomum hæmatobium* are found as a urinary sediment with tolerable frequency. They are oval, from 0.12 to 0.13 mm. long and from 0.04 to 0.05 mm. broad, and are characterized by a sharp point at one end, or by being armed with a pointed spine on the side.†

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\* For further information see J. Vogel, Krankheiten der harnbereitenden Organe, in Virchow's Pathologie und Therapie, Band 6, S. 691, *et seq.*

† For more particulars on this point and for the symptoms which they cause, see Bilharz, Zeitschrift f. wissensch. Zool., iv., p. 59, 73, and 454. The same author, Wiener medic. Wochenschr., 1856, Nr. 4 and 5.

T. R. Lewis\* found in the urine and blood of several persons suffering from chyluria in Calcutta a peculiar entozoon (named *Filaria immitis* by Cobbold).†

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\* Centralbl. f. d. med. Wissenschaft., 1873, No. 21 and 30.

† For an account of a few other entozoa which are passed with the urine in very rare cases, the reader is referred to our work on the Diseases of the Urinary Organs, in Virchow's Pathol. und Ther., Band 6, p. 555.

## DIVISION SECOND.

### QUANTITATIVE CHANGES IN THE URINE.

#### § 119.

MUCH less attention has been paid by the practitioner, until quite recently, to the quantitative changes of the urine, especially the increase or diminution of the normal constituents, than to the qualitative changes of this fluid previously considered. The reason of this was partly because generally less importance has been hitherto attached to the chemical element in disease and in the changes of metamorphosis, and partly because the methods formerly used in such investigations were very difficult, tedious, and lengthy, requiring much apparatus, indeed frequently a complete laboratory, so that they were employed almost exclusively by chemists. By the recent introduction of new methods, however, especially the volumetric methods, many of the investigations of this sort have been greatly simplified, so that they may now be performed by the practitioner quite quickly, and without any large amount of apparatus. At the same time the importance, necessity even, of the quantitative estimation of the various processes of metamorphosis in disease becomes evident; and it is to be hoped that in proportion as the importance of such investigations for purposes of diagnosis, prognosis, and treatment are brought out more distinctly, practitioners will avail themselves more frequently of them. I trust the following attempt to demonstrate the importance of such investigations to the practitioner, as far as it is possible at the present time, will assist somewhat in bringing them into more general use.

The quantitative changes of the urine may be divided into two groups, according as they are more or less readily determined.

I. Those which may be discovered without an exact chemical analysis, and which, on account of their easy detection, are of especial value to physicians.

II. Those which require a quantitative chemical analysis to detect them, and whose determination is, therefore, more difficult and complicated.

#### I. THE QUANTITATIVE ALTERATIONS OF THE URINE WHICH ARE EASILY DEMONSTRATED.

Under this head belong: The quantity of the urine; the solid residue, and the specific gravity of the urine; and the color. The estimation of all of these is so easy, requires so little apparatus and so little time, that no practitioner is excusable for neglecting them in those cases in which they may contribute something to the more complete insight into a diseased process.

##### § 120. QUANTITY OF URINE.\*

The process proposed for estimating the quantity of urine has been already described in § 57. It is most easily determined by measurement; the determination by weight is more laborious.

The estimation of the quantity of the urine is only of value when we also know the time during which it was passed. It is best to collect the urine which has been passed either during twenty-four hours, or during every hour, or at least to calculate the quantity passed for this period. In accurate estimations of the quantity of urine it is absolutely necessary that the physician should assure himself that all of the urine passed has been really collected, that none of it has been lost at stool or in any other way, and that no water, etc., has been poured into the urine vessel.

A simple estimate of the quantity of urine, without weighing or measuring it, may sometimes give the physician important indications in certain cases, but it does not serve for accurate investigations. Since graduated urine-glasses can be easily and cheaply obtained at the present time, and since they are, moreover, much better adapted for displaying the color, trans-

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\* J. Vogel, *Archiv für gemeinschaftliche Arbeiten*, Band I., p. 104, *et seq.*

parency, sediment, and other characteristics of urine, than porcelain or earthen vessels, the physician should give them the preference in all cases in private practice in which the examination of the urine is important.

In order to ascertain the average quantity of urine passed in chronic diseases (the quantity in an individual case), we must not be satisfied with measuring it for a single day; for during that short period accidental influences may easily increase or diminish the quantity. The urine must rather be measured for several days in succession and the average be taken for twenty-four hours.

To ascertain the influence of any temporary circumstances it is best to calculate the quantity of urine passed per hour.

The determination of the quantity of the urine forms the basis of the quantitative estimation of all of its constituents. It is also in itself important oftentimes in showing the activity of the kidneys, and especially their power of separating water from the system.

In many cases it is important to the physician to determine the relation of the quantity of urine to the amount of the pulmonary exhalation, perspiration, and fæces; for many hints are thus obtained which may be of service in judging of the state of the disease, in giving a prognosis, and in recommending the treatment. Thus, in most chest, heart, and skin diseases a diminution of the urinary secretion, with an accompanying increase of the pulmonary exhalation, is an unfavorable sign, and the duty of the physician in such cases is to increase the urinary secretion, in order to relieve the diseased organs. Conversely in most diseases of the kidneys, at least in their commencement, our object is to lessen the activity of the kidneys and diminish the quantity of urine by stimulating the other secretions.

When the urine is permanently much increased (polyuria, diabetes), the determination of its quantity is the first and most important means of ascertaining the nature of the disease.

To determine in any given case whether the quantity of the urine is increased or diminished, it is not sufficient merely to measure the urine; we must also know how far the amount found exceeds or falls short of the normal quantity. We must, therefore, learn the normal quantity passed by the individual.

If very accurate determinations are required, as for example in physiological experiments as to the influence of different agents on the urinary secretion, the normal quantity of urine passed by the individual must always be ascertained by trial at the time of each experiment. In investigations on the sick, on the other hand, we must, as a rule, be content with approximate determinations, and substitute for the amount of urine of the *individual*, which usually cannot be determined, the *average* quantity determined by numerous observations on different individuals.

In practice, however, little attention is oftentimes paid to this principle; because, on the one hand, physicians are apt to trouble themselves too little with such investigations, and hence deduce from observations, quite correct in themselves, false conclusions on account of judging them by an incorrect standard; and, on the other hand, over-exact physiologists unjustly reject approximate investigations made on patients, because they do not appear to them to be sufficiently accurate. It seems desirable, therefore, to illustrate this subject by a few examples.

We know that the average quantity of urine passed by an adult in health in an hour amounts to from 60 to 70 cc., but that it may vary between 30 and 100 cc. If now we find that in an individual, the normal amount of whose urine we are not acquainted with, an average hourly quantity of 80 cc. is passed under the influence of some medicinal agent, we may fairly conclude that the medicine employed had a diuretic effect; the conclusion, however, is not absolutely certain, because, as we have seen, 80 cc. are within the limits of the normal variation in the quantity of urine. Still less are we able from this experiment to decide to what extent the urine has been increased by the medicine employed, because the ordinary amount of urine passed by the individual may be either somewhat above or below the average. To obtain a trustworthy result in such a case we must ascertain as accurately as possible, by very numerous observations, the average quantity of urine passed by the individual at the time of the experiment, and then compare the quantity thus obtained with the quantity passed under the influence of the medicine.

If we find, after repeated trials, that a person who has par-

taken largely of fluids (water, tea, etc.) passes an average of 400 cc. of urine per hour, we may be assured, without accurately knowing the normal quantity of urine passed by the individual in question, that the fluids which have been taken by him have had a diuretic effect. The 400 cc. of urine which are passed per hour are so much in excess of the average quantity that it becomes a matter of no importance whether the average quantity passed by the individual is 40, 60, or 80 cc. per hour.

Quite the same thing often occurs in patients. The average quantity of urine passed in twenty-four hours by healthy, well-nourished adults amounts to from 1,400 to 1,600 cc.; in those who drink a smaller amount of fluid, 1,200 to 1,400 cc. If, therefore, we find that a patient passes only 400 cc. in twenty-four hours, we may be sure that the quantity of his urine is essentially diminished; the diminution is so considerable that it is a matter of small importance to ascertain whether the normal quantity of urine passed by the person in question is 1,200 or 1,400 cc. We may conclude, with equal certainty, that the amount of urine is abnormally increased in a patient who passes 2,500 or 3,000 cc. of urine in twenty-four hours, although we have not accurately measured the normal quantity of urine passed by that individual.

Numerous observations show that in healthy adults the average quantity of urine passed is—

- a. In twenty-four hours :  
By well-nourished persons who drink abundantly,  
from . . . . . 1,400 to 1,500 cc.  
By those who drink less . . . . . 1,200 to 1,400 cc.
- b. In one hour :  
By those who drink freely . . . . . 60 to 70 cc.  
By those who drink less freely . . . . . 40 to 50 cc.

If we calculate the average quantity of urine for the *weight of the body*, we find that an adult passes an average of 1 cc. of urine per hour for each kilogram (= two pounds) of the weight of his body.

Calculating according to the *height of the body*, we find that an adult passes hourly 40 cc. on an average for each 100 cm.



People who do not lead very regular lives are the subjects of very considerable fluctuations in the daily and hourly quantity of urine.

The daily quantity may vary between 1,000 and 3,000, and the hourly quantity between 20 and 200 cc.

These variations depend in great measure upon different external influences, upon the food, and especially upon the drink, and upon an increase or diminution of the perspiration ; and in persons who live regularly the variations are confined within much narrower limits than in those who live irregularly.

Moreover, we observe tolerably constant variations in the hourly quantity of urine at different times of the day. In this country (Germany) the average hourly quantity of urine is greatest in the afternoon hours, after the chief meal or dinner (77 cc. in an hour) ; it is the smallest during the night (58 cc. in an hour), and a medium quantity is passed in the forenoon (69 cc.). We must, therefore, in all cases in which we wish to determine accurately the influence of any agent upon the secretion of urine, take into consideration the time of day at which the experiment was performed.

It is very difficult to answer the question as to what influences increase or diminish the quantity of the urine, and chiefly because a large number of agents are simultaneously at work increasing or diminishing it, and these aid or neutralize each other, so that it is very difficult to isolate and determine the amount of each single influence.

The secretion of urine is decidedly increased by free drinking, though certainly not to the extent asserted by Falk, who stated that the whole quantity of water drunk is separated by the urine. We all know that a person who drinks a great deal, when exposed to a high temperature, and at the same time takes considerable exercise, sweats profusely, and accurate experiments have shown that under such circumstances a larger portion of the water taken passes out of the body through the skin than through the kidneys. The most different fluids, such as ordinary water, carbonated water, beer, wine, tea, etc., when taken in sufficient quantity, act as diuretics on people in health (but not always in disease) ; undoubtedly, however, the differences which exist in the diuretic action of the different fluids are very difficult to determine accurately, since a large number

of very variable circumstances modify their action, and, moreover, individual peculiarity plays an important part.

*Examples.* The quantity of urine passed per hour in healthy men was increased by plentiful drinking of water from between 60 and 70 cc. to 300, 400, 600 cc., and even more.

In twelve students, who, for the sake of experiment, drank large quantities of beer, the average quantity of urine secreted per hour amounted to 473 cc.; the minimum quantity was 212, the maximum 838 cc.

C. Westphal\* and K. H. Ferber† found that the exhibition of water increased the secretion of urine in dogs as well as in man, the secretion gradually increasing remained stationary for some hours and then returned to the normal standard. They also found that the whole of the water which was drunk was not eliminated with the urine, but that a very considerable portion of it always passed off with the perspiration.

The quantity of urine is diminished by lessening the absorption of fluid (abstaining from drink until great thirst is experienced), but not in the same degree that it is increased by free drinking.

*Example.* Four male individuals from 20 to 25 years of age were placed on dry diet. The average hourly quantity of urine which they passed, which with ordinary diet was 86 cc., sank to 37 cc. (Mosler.)

All causes which aid the elimination of water from the body by other channels diminish the secretion of urine; especially copious sweating, abundant watery stools, and much vomiting.

On the other hand, all causes which lessen the other watery secretions of the body increase the quantity of the urine: much atmospheric moisture, which impedes cutaneous and pulmonary exhalations, and other agents, such as cold, which diminishes the cutaneous perspiration.

Causes of this sort seldom exert an unmixed influence, so that the quantity of urine which is observed in such cases can seldom be regarded as a standard of the action of a particular agent. For this reason I shall omit numerous examples which I might quote. To obtain a general idea of the activity

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\* Virchow's Archiv, 1860, Band 18, p. 509, *et seq.*

† Arch. d. Heilkunde, 1860, i., p. 244, *et seq.*

of these influences the following considerations may be of service. The quantity of water passed with the urine is about equal to the whole amount eliminated by the skin, the lungs, and intestines, taken together. If, therefore, an increase or diminution of one of these latter functions is to exercise a considerable influence on the amount of urine, it must necessarily be quite a large one.

The intensity of the activity of the kidney, doubtless dependent on the nervous system, exerts a very decided influence on the quantity of the urine, especially the amount of blood pressure existing in the vessels of the kidney. This is generally greater during great bodily and mental activity, and lessened during rest and sleep. It is also increased and diminished by different diseases.

A very large number of observations made on seven men gave as the average quantity of urine passed in the night 58 cc., and on the other hand 73 cc. as the average during the day. That rest alone was the only cause of this difference is shown by the fact that persons who work during the night, either bodily or mentally, pass as much urine then as they do during the day.

The influence of increased action of the kidneys on the secretion of urine is strikingly shown in cases of dropsy. In a dropsical patient who passes on an average only 400 cc. of urine in twenty-four hours, the secretion under the influence of diuretics or even by the simple increase of the general strength may reach in a very short time 3,000 or even 5,000 cc. per day, without any essential change in the mode of life, quantity of drink, etc.

If we attempt to formularize the different influences on which the quantity of the urine depends, it may be expressed about as follows :

*The factors which especially determine the quantity of urine secreted are :*

1. *The more or less watery condition of the blood.* The quantity is increased by a free addition of fluid to the blood, and it is diminished by an abundant separation of water.

2. *The excretory activity of the kidneys.* This is certainly not a simple force ; it depends on the degree of arterial blood pressure generally, and especially on the tension in the renal arteries, particularly the glomeruli ; on the greater or less ease with

which the urine flows from the tubules; on the state of the nervous system generally, and on the state of the renal nerves in particular, etc. All of these different forces, however, have not yet been accurately determined; we, therefore, group them all under the above general expression.

*Quantity of Urine in Disease.*

The quantity of urine passed by the sick frequently varies much from the normal. These deviations are sometimes more of an accidental nature dependent on various causes; sometimes they are constant and essential, so that they are always the same in diseases of the same kind. The abnormal states of the urine of the latter class are of great importance to the physician in regard to diagnosis, prognosis, and treatment. The most important of these are the following:

1. *At the height of all acute febrile diseases* the quantity of urine is considerably diminished, except in a few rare instances, as during the paroxysms in most cases of intermittent fever, but it increases again when the intensity of the disease has passed. During convalescence the quantity of urine becomes normal or even exceeds this point.

Hence in all such diseases the quantity, especially in connection with the color (see § 122) of the urine, gives important indications. Thus a constant daily diminution of the quantity of the urine indicates that the intensity of the disease is increasing—a continued low quantity of the urine (below 800 cc. per diem) shows that the intensity of the disease has not diminished—while a steady increase of the quantity of urine shows that the force of the disease has been broken.

An explanation of this general law, which is of importance as regards the state of metamorphosis in febrile diseases, can not be given as yet. A careful examination of the urine in all of these cases shows that the diminution of the quantity of urine depends almost exclusively on a diminished *separation of water* by the kidneys; in what way this is brought about, whether by diminution of the blood pressure, by lessening of the nervous influence, or by some other unknown circumstances, we do not venture to determine.

This diminution of the quantity of the urine, with very few exceptions, takes place in all acute febrile diseases, as pneumonia, pleurisy, typhoid fever, rheumatism, gastritis, pyæmic

fever, etc., and every physician has so good and frequent an opportunity to observe it, that examples appear to be quite superfluous. The following will serve to show the progress of the urinary secretion in such cases.

A., an attendant in my clinic, whose normal quantity of urine had been accurately determined for a long time beforehand, became ill with typhoid fever. The quantity of urine which before averaged about 1,800 cc. daily, constantly diminished during three days until it reached 200 cc.; in the next five days it gradually increased up to the normal amount, and then it increased beyond this to 2,200 cc., and finally gradually returned to the normal standard.

In a patient suffering with pneumonia the quantity of urine at the beginning of the sickness diminished to 500 cc., then it constantly rose in the course of ten days to the normal standard, exceeded this, and reached 3,000 cc., when it gradually returned to the normal amount and with slight variations remained normal.

2. Toward the *fatal* termination of diseases both acute and chronic, the quantity of urine frequently either constantly diminishes, or it remains very low for a long time with variations. This, however, is not always the case: sometimes the quantity of urine diminishes only a little up to the time of death (it remains over 800 cc. per diem). This, without doubt, is due to the fact that in many cases the immediate cause of death is a gradual failure of nutrition; while in other cases it is suddenly brought about by nervous disturbances, interference with the pulmonary or cardiac movements, etc.

3. The quantity of urine passed in *chronic* diseases, especially in *dropsy* and in those cases which are classed under the common name of *diabetes* (better *polyuria*), is of especial importance to physicians.

As a rule, in dropsical patients, the quantity of urine, and especially the separation of water by the kidneys, is essentially diminished. As a result, its constituents, which should be eliminated, especially water, are retained in the blood, and either the exudation of watery fluids into the cellular tissue, serous cavities, etc., is favored, or the absorption of fluid already present is rendered more difficult. Experience shows that persons suffering from dropsy are cured more especially by increasing

the secretion of urine (diuretics); and the greater or smaller amount of urine, as a rule, in dropsical patients, is not only the safest guide in making the prognosis, but it also furnishes indications for treatment.

We usually designate with the name of diabetes those diseases in which the quantity of urine, for a long time, largely exceeds the normal standard. To judge of these cases, however, it is necessary to ascertain the amount of the solid constituents contained in the urine, and not merely the quantity. (Compare the following section.)

In many cases of polyuria the nervous system evidently has a great influence on the increase of the urinary secretion.\*

4. It is self-evident that in the sick all those things must be taken into account which may have an influence on the quantity of urine in health. Thus, in disease, the quantity of the urine may be temporarily increased by free drinking, by a watery condition of the blood in combination with an increased activity of the kidneys. More frequently it is diminished. Temporarily, by sweating, diarrhoeas, and other watery evacuations; permanently, as a rule, in consequence of their taking less food than people in health, and because the metamorphosis in general is diminished.

## § 121. SOLID RESIDUE AND SPECIFIC GRAVITY OF THE URINE.†

1. The methods of estimating the quantity of the solid residue of urine, its amount of water, and other constituents which volatilize at 100°, have been already described in § 59. The processes given there, however, are both tedious and difficult, so that they can seldom be used practically; still we must employ them in all cases in which as accurate an estimation as possible of the quantity of water or of the solid residue of urine is required.

For the purposes of the physician, who only requires approximate results, these processes may be replaced by a determination of the specific gravity of the urine, and from this its amount of solid constituents may be inferred. This method of deter-

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\* See W. Ebstein, *Deutsch Arch. f. klin. Med.*, 1873, xl., p. 344, *et seq.*, and F. Mosler, *Virchow's Archiv*, 1873, lvi., p. 44, *et seq.*

† J. Vogel, *Archiv für gemeinschaftliche Arbeiten*, i., p. 419, *et seq.*

mining the specific gravity has been explained in § 58. For the physician's use the so-called urinometer, a glass hydrometer, is the most convenient, as it may be simply allowed to sink in the urine which is to be tested. (See page 212.)

If the urine were a fluid which, independently of its variable amount of water, always contained the same constituents in the same proportion, we could estimate with tolerable accuracy its quantity of solid constituents from its specific gravity, just as the percentage of alcohol or of sulphuric acid is ascertained. Unfortunately this is not the case, the quantity of the different constituents of the urine increases and diminishes in very variable proportions; therefore we cannot obtain from the specific gravity of the urine accurate results as to the amount of solid constituents, but they are always more or less uncertain. The best formula by which to reckon the quantity of solid constituents in the urine from its specific gravity is Trapp's. It consists in doubling the two last figures of the specific gravity obtained. The product gives the number of grams of solid constituents contained in 1,000 cc. of the urine in question. Thus, a urine of 1.010 specific gravity contains 20 gm. of solid constituents in 1,000 cc.; of sp. gr. 1.015, 30 gm.; of 1.020, 40 gm., and so on.

In order not to draw erroneous conclusions as to the amount of solid constituents from the specific gravity of a urine we must first of all bear in mind how great the accuracy of this method is, and also how great is its liability to error. Numerous experiments made by myself, and comparison with the observations of others, have shown me that, in estimating the solid residue of a urine from its specific gravity in specimens of normal urine, we may easily have an error of one-tenth, or even one-seventh; and in the urine of the sick, especially when the specific gravity is high, the error may be even greater, amounting to one-fifth or one-quarter. If in three successive days there are found 55, 50, and 60 gm. of solid constituents according to Trapp's formula, these differences are so slight that they fall within the limits of error in the observations, and we should not be justified in saying that the patient on the day on which the calculation gave 60 gm., passed the most solid constituents with the urine, and on that in which 50 gm. were found, the least was passed. Such a conclusion would only be justified



when the quantity of solid constituents of the urine had been determined by a more exact method. If, on the other hand, we find from the specific gravity that a person who has passed, on an average, about 60 grm. of solid constituents with the urine, secretes on one day only 30, we are perfectly justified in concluding that he has passed on that day much less solid material than usual, since the difference is so great that it cannot be explained as an error of observation. On the other hand, it would be very rash to assert that the person in question had passed only one-half the ordinary quantity of solids, and it is only to be regarded as approximate, since a direct determination would give, perhaps, 28 or 36 instead of 30 grm.

Since all such determinations of the solid residue from the specific gravity give such inaccurate results, it appears to be quite immaterial whether we make use of Trapp's coefficient (2) or of a different one (for example, Häser's = 2.33, or of Christison's = 2.3), since the difference between them (between Trapp's and Häser's is only one-sixth) still comes within the limits of unavoidable errors of observation.

W. Kaupp\* also found Trapp's formula correct, while the accurate investigations of Neubauer (see page 221, 3, and page 347) are more in favor of Häser's formula. For estimations and conclusions at the bedside of the patient, which can never be very exact, the coefficient 2 commends itself by its simplicity and the readiness with which it can be reckoned in the head. In such cases differences in the temperature of the urine, if they do not exceed a couple of degrees, may be disregarded.

2. What practical conclusions can the physician draw from the quantity of solid residue and the specific gravity of the urine?

First the specific gravity enables us to calculate the weight of a measured quantity of urine. The calculation is simple: 1.000 cc. of urine of specific gravity 1.024 weigh 1.024 grm., and so on.

Further the specific gravity of the urine and the quantity of solid constituents found either directly by analysis or calculated often give important indications concerning many quantitative changes of metamorphosis; especially in the quantity of solids and of water, which have been separated by the urine under certain circumstances in a certain time.

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\* Archiv für phys. Heilkunde, 1856, Heft 4.



To judge of these conditions it is of prime importance for us to know the exact normal.

The average specific gravity of the urine in male adults in the normal condition is about 1.020. From this we may reckon that in an average daily quantity of urine of 1,400 or 1,600 cc., an average daily quantity of 55 or 65 gm. of solid constituents are eliminated.

A man passes on an average 4.1 gm. of solid constituents per 100 kilograms of weight and 1.5 gm. per 100 centimeters of height per hour.

These figures form the basis for recognizing and forming an opinion of many abnormalities of the metamorphosis in disease.

In most acute diseases the daily separation of solid constituents by the urine is somewhat less than in health; instead of 60 it amounts to only 40 or 50 gm. Since such patients as a rule, however, only take fluids which contain little solids, they are in a condition similar to that of persons fasting, the separation of the solid constituents of the urine takes place in them at the expense of the body, they consume their own flesh, as it were, and become thin.

The estimation of the amount of solid residue of the urine is of especial practical interest in all cases in which the secretion is much increased in quantity (polyuria). These cases may be separated into two well-marked groups according to the greater or less quantity of solid constituents contained in the urine.

1. The abundantly secreted urine contains much more solid material than in the normal condition, much more in fact than is introduced into the body by means of the food. Hence arises a disproportion of nutrition, the patients in question become weak and emaciated. The cases belonging to this group are included under the further subdivisions according as the urine contains sugar (diabetes mellitus), or is free from it but contains an abnormally large amount of the other solid constituents (diabetes insipidus).

2. The excessively abundant urine has a low specific gravity and contains relatively few solid constituents. Water is the constituent which is chiefly separated from the body by it, and it is very readily restored again; no emaciation results, therefore, and no hectic; on the contrary, the process is sometimes beneficial, and promotes the removal of diseased products, as in

many cases of hydræmia and dropsy. This form of increase of the urinary secretion (hydruria) must, therefore, be most carefully distinguished from true diabetes.

*Examples.* A woman, 31 years of age, who had suffered for a long time from symptoms of anæmia and hysteria, with giddiness, headache, spasms of the cervical muscles, sensitiveness of several of the vertebræ, pale face, etc., passed an increased quantity of urine (the average of a fourteen days' observation amounted to 3,080 cc. daily). The specific gravity of the urine was only slightly diminished, and the calculated quantity of solid constituents in it amounted to a daily average of 87 gm., a quantity much greater than normal (the maximum in 24 hours was 136 gm., which was more than double the normal quantity). In this case, which was one of true diabetes insipidus, the increased separation of the solid constituents of the urine combined with a deficiency of nourishment was evidently the chief cause of the symptoms, which rapidly improved under a more generous diet in addition to the use of iron and other tonics.

A man, 35 years old, of herculean frame, suffering from rheumatism of the neck, passed a very large quantity of urine (the daily average of observations lasting twenty-four days was 2,983 cc.), but its specific gravity was very low (between 1.005 and 1.012), and the daily average amount of solid constituents reckoned from it amounted only to 42 gm., therefore less than normal. This man did not appear to suffer at all from the increased secretion of urine; it evidently was not diabetes, but merely hydruria.

Many other conclusions concerning the quantitative changes of metamorphosis in disease may be drawn from the specific gravity and quantity of the solid constituents of the urine; thus, for example, the relation of the amount of solid constituents which are eliminated with the urine to that of those which are eliminated by the skin and lungs may be ascertained; when the quantity of solid matters taken with the food is known at the same time, we obtain the relation of the amount which is taken into the body to that which passes out of it, etc. The knowledge of all of these points is of great importance in relation to the metamorphosis in disease, and the necessary means are of such a nature as to be procured in every clinic without

difficulty; but so little has been done thus far in this field that no special conclusions have been drawn as yet.

The specific gravity of the urine, moreover, gives the physician indications which, though of themselves not sufficient to lead to any definite conclusions in diagnosis, prognosis, and treatment, are yet serviceable by leading to further investigations. The following considerations belong under this head:

Urea is the chief solid constituent of the urine as a rule; it usually equals all of the others together and sometimes exceeds them. Therefore, the specific gravity of the urine may also serve to point out approximately the quantity of urea contained in it. Such an estimation of the quantity of urea is, however, very uncertain, and considering the ease with which it may be directly determined quantitatively it will never replace the latter method.

When urine is far below the normal in quantity and has a high specific gravity, we may generally infer in the case of healthy persons that its condition depends on abstinence from drink or upon an abundant loss of water by increased perspiration; and in the case of disease it depends on an acute disease. When the amount of urine is increased far beyond the normal and the specific gravity is low, we may conclude that an excess of fluid has been taken. In the sick who are suffering from hydræmia or dropsy such a condition of the urine is a very favorable sign, and indicates that the system is making an effort to get rid of the excess of water collected in the blood or tissues.

If a superabundant amount of urine of high specific gravity is passed, or if it has only the ordinary specific gravity, we must bear diabetes mellitus in mind and test for sugar; or, when it contains no sugar, the case is diabetes insipidus.

If the quantity of urine is not increased, or if it is diminished even and yet its specific gravity is low, we may suspect the existence of some impediment to the secretion of urea, and have reason to fear the results of retention of urea in the body (uræmia) in such a case.

In most chronic diseases (except diabetes) the solid residue of the urine is diminished; an increase of the solid residue indicates a more active metamorphosis and better nutrition, and is, therefore, a favorable sign as a rule.

On the other hand, an increase of the solid residue of the

urine at the height of acute diseases is usually an unfavorable sign, because the inanition, which always occurs in such cases, is thereby increased and favored.

The specific gravity of the urine, as a rule, in acute febrile diseases, is in inverse proportion to its quantity; the specific gravity increases at the height of the attack in proportion as the quantity diminishes; it afterward falls with the increase of the quantity, and sinks during convalescence frequently below the normal. We must be careful, however, not to infer too much from the specific gravity of the urine alone, and not to utilize it, for example, for the differentiation of diseases which in other respects present similar symptoms.

It has been stated that the specific gravity of the urine increases much less in typhoid than in other acute diseases, and especially in inflammatory diseases; and that in the true typhous stage it amounts to only 1.017, while in acute affections of the brain, especially meningitis, from the beginning to the end, it is much higher (1.028 to 1.035). This difference, therefore, may be utilized in cases where it is difficult to distinguish between a typhoid and such affections of the brain.\* Such an attempt to distinguish diseases by a single phenomenon, and one which, in comparison with the other symptoms, is very unimportant, belongs to the now happily ended ontological method of comprehending diseases. In the distinction and classification of diseases by this method, just as in the division of animals and plants into genera and species, only the external appearance with its thousand accidents is regarded instead of their essential character, their causes, connections, and interdependence being kept in view. Such a use of a single symptom can only be justified, when not only the fact itself has been surely established by numerous observations, but also its cause and signification have been explained, and its necessary relation with the disease in question.

In the case before us, there is wanting not only a satisfactory explanation of the diminution of the specific gravity of the urine in typhoid, but also the truth of the fact, except in isolated cases, is only problematical. According to my very numerous investigations of the urine of typhoid patients, its

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\* A. Ziegler, *Die Uroscopie am Krankenbette*, Erlangen, F. Enke, 1861, p. 8.

specific gravity, at least in the cases in which considerable fever and a certain degree of reaction is present, was high during the acme of the disease, as the following cases show :

(The figures in all cases show the specific gravity of the whole quantity of urine passed in twenty-four hours during the height of the disease. The blanks, which sometimes cover several days, arise from the impossibility of always collecting the whole quantity of urine passed, unmixed with *fæces*, in patients who frequently pass urine involuntarily with their stools. This is a circumstance which renders accurate quantitative examinations of the urine in typhoid at the height of the disease difficult or even impossible.)

Case 1. Third day, 1·019—1·029—1·031—1·026—1·024—(two days omitted)—1·019—1·021—1·016. Subsidence of the fever. Convalescence.

Case 2. Fourth day, 1·028—1·029—1·027—(one day omitted)—1·028—1·027. Death.

Case 3. Second week, 1·019—1·020—1·018—1·020—1·022—1·026. Slow convalescence.

The specific gravity of the urine in typhoid, as in other acute diseases, falls as the fever diminishes and convalescence is established.

On the other hand, I must admit that there are cases of typhoid in which the specific gravity of the urine, even during the height of the disease, is low, sometimes even far below the normal, as the following examples show :

Case 1. 1·008—1·014—1·017—(two days omitted)—1·017—1·027—1·015—1·014—1·015—1·014—1·012. Death.

Case 2. First week, 1·018 to 1·020. Second week, 1·012 to 1·015 ; then convalescence.

Case 3. 1·021—1·020—1·015—1·014—1·010—1·006—1·010—1·012—1·013—1·015—1·011. Convalescence.

In all of these cases, however, the fever from the first had a distinctly marked adynamic character, and the general condition of the patients, especially the weak and distinctly double pulse, afforded much more trustworthy signs for distinguishing the case from one of inflammatory affection of the brain and its membranes than the specific gravity of the urine, which, moreover, I have not always found so remarkably high in meningitis as Ziegler states it to be. Such a diminution of the spe-

cific gravity of the urine, moreover, does not occur exclusively in typhoid; it also occurs in other forms of fever, when they assume a well-marked adynamic character, as in pyæmia, putrid fevers, etc.

### § 122. THE QUANTITY OF URINARY PIGMENT.\*

The color of the urine and the pigments which cause it have been already spoken of in various places (§ 10, § 61, § 93). It is very difficult, indeed almost impossible, to obtain an accurate estimation of the quantity of coloring matter in the urine corresponding to the requirements, which we are entitled to expect of quantitative chemical analysis at the present day. I have, therefore, proposed another method, very simple and easy, of determining this substance quantitatively, so that every practitioner can avail himself of it. Although the results are not absolutely exact, but are merely approximate, they afford much that is interesting and valuable for diagnosis, prognosis, and treatment.

This method, and the mode of employing it, has already been explained in § 61, and the color table in Plate IV. gives every one an opportunity of using it himself.

As objections to this method, since its proposal, have been made by various writers, I will briefly answer them.

First, it has been objected that the color of the urine does not depend on *one* and the same pigment, but on several different ones. This is correct, and has been already admitted in § 93. But the abnormal colors of the urine described there, whether they are merely accidental, depending on the pigments of rhubarb, senna, etc., or whether dependent on biliary pigment, uroxanthin, uroglauclin, urrhodin, and uroerythin, are relatively rare, and, when present, may be readily recognized. In all such cases it would doubtless be a mistake to use the color table for the quantitative estimation of the urinary pigment. But these are exceptional cases for which the method is not adapted; and it can be no reproach to it that this is the case, for it very rarely happens in other quantitative chemical investigations that a method is applicable to all cases. In by far the greater number of cases the urine, especially when it has

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\* J. Vogel, Archiv für gemeinschaftliche Arbeiten, i., p. 187.

been filtered, contains either none, or only a very small quantity, of such abnormal coloring matters, but is usually colored by the ordinary urinary pigment (Heller's urophæin, Thudichum's urochrom, Jaffé's urobilin).

Moreover, it has been objected that the shades of color given in the color table do not follow in an exact series, and that by diluting brown or very high-colored urine, we should not obtain exactly the same shades of color which pale urine yields; and, therefore, the statement that a red urine contains thirty-two times, and a brown red one sixty-four times as much coloring matter as a pale yellow would not be exact. I am quite ready to admit that the coloring matter of the urine is not the same thing always and under all circumstances, but that it may present modifications which exercise an influence both over its coloring power and over the shade of color produced by it; but this is no reason why we should not use the color of the urine as a means of estimating approximately the urinary pigment, if we do not assume the limits of possible error as too low. Hitherto, notwithstanding the praiseworthy efforts of Scherer, Harley, Thudichum, Jaffé, and others, we have not been able to obtain the urinary pigment in a pure state, so that the establishment of the limits of error in this case is completely arbitrary. But I believe I am rather above than below the mark, when I assume that the possible error may amount to one-fourth or even one-third of the number found. Variations which exceed these, therefore, indicate with certainty a difference in the amount of coloring matter in two specimens of urine compared with each other, while other variations which are less than these might be neglected.

If, for example, the quantity of pigment which a healthy individual passes with his urine in twenty-four hours amounts to four units, and we find that a sick person passes from sixteen to twenty, a considerable increase of the coloring matter in this case is undoubted; it is at least double or treble. There is also an undoubted diminution, if the calculation gives only one. But if, on the other hand, we should find three and a half or four and a half, we cannot conclude with certainty that there has been a diminution or an increase.

On these grounds I consider that I may maintain that this method, carefully employed, may give useful results, and that



(for the reasons given in the following explanation of its significance) it may give the physician very important information as to the metamorphosis, or the destruction of blood corpuscles, information which appears the more valuable because the means which the physician possesses of forming an opinion as to the extent of this kind of metamorphosis in the sick is very limited.

The *indication* which an increase or diminution of the urinary pigment affords to the physician may be derived from the following considerations, which indeed are not proved, but are in part hypothetical, and yet are probably correct.

There is much reason to believe that a portion of the blood corpuscles in the living body is constantly undergoing a retrograde metamorphosis and being dissolved, so that its coloring matter, hæmatin, is so changed that it finally passes out of the body in the form of urinary and biliary pigment; therefore, we have in the amount of the coloring matters of the urine and bile taken together a sort of measure of the degree of decomposition of the blood corpuscles. From it, in many cases of disease, the physician can obtain valuable hints and conclusions respecting diagnosis and treatment.

It is too soon now to be able to determine how much blood pigment or how large a quantity of blood corpuscles a certain amount of urinary pigment corresponds to. We know too little as yet about the changes which blood pigment undergoes before it becomes metamorphosed into urinary pigment. For this reason I have preferred to take as a standard of comparison for ascertaining the amount of urinary pigment an imaginary quantity, by fixing 1 as the quantity of urine pigment which 1,000 cc. of pale yellow urine contains, instead of attempting to ascertain the quantity of the coloring matter absolutely by weighing or by comparison with the color of a known quantity of blood corpuscles, such a determination in a short time being too difficult.

The reasons for the above hypothesis, that the urinary and biliary pigments are modified blood pigment, are as follows: Blood coloring matter is very difficult to destroy; we see that extravasations of blood in the body, as well as blood which has been subjected to various influences outside of the body, retain their color with great tenacity, or only undergo slight modifications



of color. It is not probable, therefore, that the coloring matter of the blood which has become unfitted for the purposes of the economy is eliminated from the body as a colorless substance, but, on the contrary, there can be scarcely any doubt that it is still more or less colored when it is excreted. Since the only colored excretions of the body are the urine and the stools, we must consider the urinary pigment or the biliary pigment (as it appears modified in the fæces), or both, as formed from the used-up blood pigment. For these reasons many thorough observers, as Scherer, Polli, Virchow, Harley, and others, have not hesitated to regard the biliary coloring matter, the urinary pigment, or both, as in part educts of the hæmatin. Moreover, some observers (Hoppe-Seyler, Maly) have recently succeeded in transforming blood pigment (hæmoglobin) by chemical treatment directly into biliary pigment (bilirubin) and urine pigment (urobilin). (See page 64.)

The quantity of urine pigment which an adult passes normally in twenty-four hours amounts to from 3 to 6 units, or an average 4·8, therefore about 0·2 in an hour, the above unit being taken as the standard.\*

According to R. Lawson† a much greater quantity of pigment is passed with the urine in the tropics (Jamaica), as a rule, than in our latitudes: 12 to 14 times the above unit in twenty-four hours in healthy men.

This is the standard for judging the quantity of pigment in the urine in a given case of disease, whether it is normal, increased, or diminished.

The quantity of urinary pigment is considerably increased in all acute febrile diseases in spite of the fact that, at the same time, there is a diminution in the amount of urine; it usually reaches 16, 20, and more. This increase in the urinary pigment is still greater in fevers which are accompanied by dissolution of the blood (typhoid, septic fevers).

We observe as a general consequence of all of these diseases

\* According to some of my investigations the quantity of coloring matter which is passed with the stools is very variable. I found during twenty-four hours from 8 to 80 parts of coloring matter measured according to the above scale.

† Some observations on the urinary and alvine excretions, as they appear within the tropics, *British Rev.*, Oct. 1861, p. 488, *et seq.*

a diminution of the number of blood corpuscles, a more or less anæmic condition of the body (more exactly oligocythæmia).

*Examples.* In a large number of patients with pneumonia the daily quantity of urinary pigment varied between 16 and 24 units during the height of the disease. In a case of acute rheumatism it amounted to between 30 and 32 when the disease was at its height; in a man suffering from typhoid it amounted during several days to between 80 and 100; in a man who had inhaled arseniuretted hydrogen, from 600 to 800. In the last case the matter which colored the urine differed somewhat from the ordinary urinary pigment, as it was nearly pure hæmatin, so that its determination quantitatively, according to the intensity of the color, could only be approximate; the difference, however, between the quantity found in these cases and the normal quantity is so very great, that an error in the estimation of one-quarter or even of one-third need scarcely to be taken into account.

On the other hand the quantity of urinary pigment in many diseases is decidedly below the normal, in those cases in which a diminished metamorphosis of the blood corpuscles must be assumed to exist; as in many cases of chlorosis and anæmia; in convalescence from severe diseases; in hysteria and nervous diseases, etc. In such cases the character of the urine frequently serves as an aid in the diagnosis and treatment, since tonics, especially preparations of iron, are usually indicated.

*Examples.* The daily quantity of urinary pigment in chlorotic persons is frequently below 1; in convalescence from severe diseases it is often for a long time not above 1 or 2, etc.

## II. QUANTITATIVE ALTERATIONS OF THE URINE WHICH REQUIRE A COMPLICATED CHEMICAL ANALYSIS FOR THEIR DEMONSTRATION.

### § 123.

The quantitative alterations of the urine considered in the previous sections are very easily determined, and their estimation requires so little practice and special knowledge, so little apparatus and accessories, that, in point of fact, it is not too much to ask that every physician should undertake the investi-

gation of them himself, in those cases where it is of importance to determine these changes of the metamorphosis and to draw conclusions from them.

The quantitative alterations in the composition of the urine which are to be spoken of now, have been hitherto much more difficult to determine; for the most part they required much time, more in fact than the busy practitioner could give to them, and presupposed special chemical knowledge and a certain practice in quantitative chemical analysis, besides requiring manifold apparatus, utensils, and reagents. Many of them, indeed, could be carried out with the requisite certainty only in a completely furnished laboratory, which is rarely at the command of a physician. Consequently, analyses of this kind have hitherto been undertaken almost solely by chemists for the solution of physiological questions, and rarely by physicians for practical purposes. Moreover, the report of such investigations has been regarded by most practitioners as no essential contribution, nor as a necessary part of the history of the disease in question, but as a superfluous embellishment; indeed, by many it is regarded as quite an unnecessary extravagance. Under these circumstances it was useless to expect physicians to undertake such investigations. Only a few voluntarily applied themselves to it, partly through love of science, and partly because they were convinced that, by undertaking them in some cases of disease entrusted to them, they might render important service.

Happily this state of things has essentially changed in the last few years. Jointly with the ever-increasing application of chemistry to the arts and manufactures grew the discovery of methods which essentially simplified and shortened quantitative chemical analyses. These methods, especially the so-called volumetric methods, are very well adapted to the purposes of the physician. This applies especially to the quantitative examination of urine. These simple methods of quantitative analysis are already completely worked out for many of the constituents of the urine, and we may hope that they will be speedily extended to the rest. In short, most of the quantitative examinations of urine, which a few years ago were difficult to perform, are now so simplified that they exceed neither the knowledge, skill, nor expedients which we may expect a physi-

cian to possess. Even want of time can no longer serve as an excuse for a physician for neglecting such investigations in cases where they are necessary, since a chemist or an apothecary can be found almost anywhere, who, for a small sum, will undertake the simplified analysis for the physician; and, in case of need, any apt attendant on the sick, or servant, if he be careful and intelligent, may be taught in a short time enough for the purpose. In many cases, indeed, the patients themselves are not only inclined, but are also qualified to undertake such investigations.

The chief point for the physician who undertakes such analyses, or causes them to be undertaken, is that he should always clearly know, as far as possible in each case, what he wishes and may expect to ascertain by the examination. Any one who is not quite clear on this point would do better to give up such investigations entirely, since, in such a case, the analysis is generally useless and often even mischievous. The chief object which has been in my mind in the following sections has been to instruct the physician upon these points, as far as it is possible to do so at the present time.

I must first, however, before considering the special investigations of the individual constituents of the urine, premise certain general rules which are more or less applicable to all such quantitative examinations. They form the contents of the next section.

#### § 124. GENERAL RULES FOR QUANTITATIVE ANALYSIS OF THE URINE.

1. Hitherto observers have usually made use of an indefinite quantity of urine for quantitative estimations, and have been satisfied when they had ascertained how much urea, uric acid, chloride of sodium, etc., etc., was contained in 1,000 parts. And at the present time, also, such analyses of the urine are quite often sent or brought to me by patients who come to consult me about themselves. From such an analysis, however, we learn nothing more than the relation which the single constituents of the urine bear to each other. It is, therefore, rarely of much service to the physician. And if such a quantitative analysis only includes a single constituent of the urine, so that we only learn from it how much urea, or uric acid, etc., 1,000

parts of the urine contain, it is wholly useless. A quantitative analysis of the urine gives a measure of the metamorphosis only when, together with the relative quantities of the various constituents of the urine, the *time* is also given during which they were passed ; so that we must not only learn how much urea, uric acid, etc., are contained in 1,000 parts of urine, but we must also know what quantity was passed in a certain time, as in twenty-four hours, one hour, etc. Hence, the first requisite in every quantitative analysis of the urine is the determination of the time during which it has been passed. This determination is very easy in certain patients. Either the urine of *one* day (twenty-four hours) is collected, when it rarely hinges on a quarter of an hour, more or less, or the patient carefully observes the quantity of urine secreted during a shorter interval. If, for example, the patient passed his urine at eight o'clock and it was not preserved, and at ten o'clock he passed a fresh quantity which was measured and subjected to quantitative analysis, we know that the whole amount of the different constituents of the urine found by the examination were derived from a two hours' secretion, and from it we can easily calculate how much urea, uric acid, chloride of sodium, etc., were passed in *one* hour, or in any given time. The determination of the quantity of the urine, and the time during which it was passed, therefore, forms the basis of all quantitative urinary analyses, and we cannot recommend the physician too strongly to pay the greatest care and attention to these fundamental determinations, because, if they are inaccurate, all attention and pains which have been expended on the analysis have been thrown away. The determination of the quantity of the urine passed in a given time is difficult and uncertain in many cases, especially in the sick ; sometimes the time cannot be accurately ascertained, more commonly an uncertain quantity of urine is lost by being passed at stool, or involuntarily when the patient is seriously ill ; often some is thrown away by the fault of the attendants or nurse while the physician is absent. The physician must know and guard against all of these sources of error, and in cases where he is not certain that they can be avoided, it is better to dispense with a quantitative analysis of the urine altogether rather than to run the risk of arriving at erroneous conclusions by starting with false premises.

2. It is very important, moreover, that the physician should know the limits of error of the different methods which he makes use of in the analysis, and should always bear them in mind when drawing his conclusions. I will give these limits of error, as far as it is possible at present, in each individual case, but do not consider it superfluous to make a few general remarks on the subject here.

The limit of error in an analytical method, that is, the quantity by which the result thus obtained may differ from the truth, depends on two circumstances : 1. On the accuracy of the method itself ; 2. On the greater or less skill and care of the analyst himself, the completeness of his apparatus, purity of his reagents, etc. The first is unavoidable, but may be determined with tolerable accuracy, and its amount shows the greater or less utility of an analytical method. The second circumstance is variable ; when the analysis is bad the error is great, when it is good it is very small indeed. We cannot expect of every physician who performs a quantitative analysis of urine that he shall be an expert analyst, but we may require him to have an approximate idea of the reliability of his analysis. Any one can readily ascertain this by repeating a quantitative estimation of the same constituent of urine several times with the same materials and following the same method. The greater or less degree of conformity which the different analyses exhibit, gives an idea at the same time of the reliability of the method employed and of the accuracy of the analyst ; it shows how far the figures he finds are to be relied upon, and to what extent his conclusions are to be accepted. If, in this way, by repeated experiment, we have once fixed the limit of error which can be committed in an analysis, we may, in cases in which great accuracy is not necessary, content ourselves with a single uncontrolled analysis. In all quantitative analyses, however, where great accuracy is required, where the material admits of a repetition of the analysis, a second analysis to control the first is always to be made, and if the results differ very much, still a third, and the average of the results is then to be taken.

Frequently cases occur where an accurate determination of the quantity of constituents of the urine is not necessary for practical purposes ; where, in fact, it is quite enough to know that a specimen of urine contains more or less than a cer-

tain amount of any constituent. A few examples will illustrate this. A healthy man passes about 10 to 13 gm. of chloride of sodium with his urine in twenty-four hours. In most acute diseases during their height the separation of the chloride of sodium by the kidneys is reduced to a minimum. If, therefore, we learn by an approximate analysis (which will be explained later) that less than 1 gm. of chloride of sodium is passed with the urine in twenty-four hours, we may conclude that there is a very considerable diminution in the separation of chloride of sodium: in many cases this is quite sufficient for the purposes of the physician, and it is of no importance to know whether the quantity of chloride of sodium amounts to 0.1 or 0.5 or 0.8 gm. A healthy man passes in an hour about 0.070 to 0.100 gm. of sulphuric acid with the urine. If we find by a simple experiment that a person passes more than 0.400 gm. in an hour, we can conclude that the separation of sulphuric acid is very much increased, and that the quantity amounts to at least four times the normal standard.

Such approximate determinations, which may be variously modified according to circumstances, have the great advantage to the physician that they can be conducted in a very short time, within two or three minutes, while an accurate estimation would require perhaps thirty or forty minutes. However, we must draw no further conclusions than those which the results warrant.

It appears from this that the quantitative analysis of urine may and must be carried out in very different ways according to our object. A physician who knows what he wants may in certain cases draw conclusions from an approximate quantitative analysis performed in a minute or two, which are more valuable to him than the results obtained by a careful analysis conducted by a skilled chemist who perhaps has devoted several days to the operation, but which is useless to the physician because just that point which he wanted to know has been omitted. This shows how important it is to keep clearly in mind the object aimed at.

3. The question as to the significance to the physician of the increase or diminution of this or that constituent of the urine will be answered under the head of each constituent. It appears advisable to me, however, to premise here a few



general remarks which are equally applicable to several constituents.

The different constituents of urine may be divided into two great classes, according to their origin.

Those of the one class are doubtless formed within the body; they are in fact the products of the activity of the body. Urea and uric acid, which are very rarely taken into the body as ingesta, belong here. A diminished quantity of these bodies in the urine always shows that they have either been produced in less quantity than normal, or that they are stored up and retained in the economy; perhaps also in a few rare cases they have been eliminated in an abnormal way, or have undergone a partial decomposition and transformation within the system. On the other hand, their increased secretion with the urine shows that they are either produced in larger quantity than normal, or that they have been stored up somewhere in the body and have all at once been eliminated.

Most of the constituents of the urine belong to the second class; they may be produced within the system in part, or be formed from other matters by chemical decomposition; some of them only go through the body, however, and whether greater or less quantities of them are passed with the urine depends in part on the varying activity of the body, and in part also on whether greater or less quantities of them are taken into the body with food, drink, medicine, etc. Thus, for example, the oxalic acid of the urine, as described in § 110, may be formed within the body from other substances, or it may have been taken in with food containing oxalic acid. The sulphuric acid of the urine may result from the oxidation of the sulphur contained in the protein substances and constituents of the body, or it may come from sulphate of calcium contained in drinking water, etc. And whether the urine contains more or less chloride of sodium, may depend upon an increase or a diminution of the action of the kidneys, or upon the addition of a greater or less quantity of salt to the food.

When, therefore, an increase or diminution of the constituents of the urine belonging to this class is found, we must be very careful in drawing our conclusions, and must only refer the cause to a change in the activity of the system or to its pathological conditions, when we are convinced that the in-

creased or diminished secretion does not depend upon a greater or less absorption. Such a conviction can only be obtained by determining quantitatively, or at least estimating approximately, how much of the compound in question was taken into the body in a given time by the different ingesta. Such investigations are very laborious and have hitherto been very rarely undertaken. Therefore, this whole subject is still shrouded in darkness, and the statements which have hitherto been made by different observers concerning the increase or diminution of single constituents of the urine in diseases must be received with a certain amount of caution.

Finally, we will allow a place here for an observation which has been omitted in previous editions as unnecessary, because it appears self-evident to every intelligent person, but which perhaps is not superfluous, since experience has taught us that it has often been neglected and still continues to be.

When we wish to determine alterations of the urine of a *general nature*, as, for example, those which are produced by certain influences, certain diseases, etc., very numerous observations are necessary as a basis, if the conclusions drawn from them are to be in a measure exact and of scientific value. Only in those cases in which all of the observations without exception show a *very* considerable deviation from the normal, and always in *the same direction*, as, for example, diminution in the quantity of urine in febrile diseases (see page 451), is a moderate number of observations sufficient. On the other hand, the less the deviations are from the normal, so that they in part fall within the limits of the necessary errors of observation, and the less these deviations follow each other in the same direction but appear sometimes positive and sometimes negative, the greater must be the number of observations instituted; and in very complicated cases, in which at the same time many influences of different sorts act on the urinary secretion, sometimes thousands of examinations do not suffice to establish a "law."

Any one, who, heedless of this precaution, inconsiderately draws conclusions from a few investigations whose results are very easily influenced by accidental circumstances, does not contribute to science, but rather brings confusion into it, and has himself to thank when he receives a well-merited rebuke.

We now turn to the special consideration of the indications presented by the increase or diminution of the different constituents of the urine.

### § 125. UREA.\*

The mode of determining the quantity of urea in the urine and the modifications of the process necessary in certain cases have been already described fully in § 65; it remains for us here only to consider the accuracy and limits of error of this method, as well as the information which may be obtained from the results.

It seems to be very uncertain, and may lead to considerable error, to calculate the quantity of urea in a specimen of urine from its specific gravity according to certain formulas as recommended by some authors, for example, Haughton. (See page 455.)

I. The estimation by Liebig's method is certainly the most convenient, and, therefore, is to be recommended, especially for the purposes of the physician. It is very accurate, so that comparative analyses undertaken with the same urine, and very carefully performed, gave a difference of less than one per cent. There are two sources of error, however, in this method of determining the quantity of urea, which in certain cases may lead to considerable inaccuracy, and they can only be avoided by quite troublesome and long modifications of the original method. They are as follows:

1. The error which depends on the presence of chloride of sodium in the urine.

This, together with the means of avoiding it, have already been pointed out on page 237, *et seq.* I have, therefore, only a few practical remarks to make on this point. In all cases in which we wish to obtain a very accurate estimation of the quantity of urea in a specimen of urine, where an error of one or two per cent. is not admissible, we must precipitate the chlorine from the urine by nitrate of silver, as described on page 238, *et seq.*, before estimating the urea.

In estimations in which so great accuracy is not required,

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\* Th. L. W. Bischoff, *Der Harnstoff als Maass des Stoffwechsels*, Giessen, 1858. Voit, *Zeitschr. f. Biologie*, Band 4, p. 77, *et seq.*

- this tedious process may be omitted; then two courses remain to us:

First, we may take *no account whatever* of the chloride of sodium which is present. We then, except in the cases where there is no chloride of sodium at all, or merely traces of it, always obtain too high a figure for the urea. The error may amount to 10 or even 20 per cent. It will be great, for instance, if we compare the urine of healthy people, which usually contains an abundance of salt, or of persons suffering from chronic diseases, with the urine of those who are suffering from acute diseases, which usually contains very little chloride of sodium.

Or we may make a correction for the amount of chloride of sodium in the urine in the quantity of urea which has been found. (See page 238.) Such a correction, however, is always merely approximate, and the error may reach as high as five per cent. and be either positive or negative.

2. A second source of error in the Liebig process is that other matters than urea may be precipitated, in which case the weight of the urea obtained will be too high.

This is true of allantoin, kreatinin, and sarkosin (see page 241); it is also true of other nitrogenous constituents of the urine, which are more frequently present, especially in the urine of the sick. Kletzinsky\* found in a number of carefully performed experiments that a nitrogenous compound, which was not urea, was precipitated by an acetate of lead solution from most urine, but in Liebig's method was precipitated with the urea and is included with it in the calculation. The quantity of this substance in the experiments of K. amounted to 4, 3, 3, 2, and 2 per cent. in healthy urine; in the urine of sick people, on the other hand, it was much greater (amounting to about 12 per cent.). Hence too high a number for the urea, especially in the urine of the sick, may be found, and this error, in many cases, can probably reach as high as 20 per cent. This error is often, to a certain extent, counterbalanced, since the urine in acute diseases may contain very little chloride of sodium, and, therefore, the amount of urea found in it, compared with that found in the urine of persons in health, without cor-

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\* See Kletzinsky, *Komparative Versuche über den Werth verschiedener Methoden der Harnstoffbestimmung*, Heller's Archiv, 1853, p. 252.

rection for the chloride of sodium, would be too small; but such compensations suffice only in very superficial investigations, and are not reliable when absolute accuracy is required.

To avoid this error, we must add to the urine under examination sugar of lead solution, rendered acid by a drop or two of acetic acid, until the whole of the substances capable of precipitation are separated; then any excess of lead is precipitated from the filtrate by sulphuretted hydrogen and the urea determined by Liebig's method.

II. What conclusions are to be drawn from an increase or diminution in the quantity of urea in the urine?

Naturally the quantity of urea which is separated under normal conditions by people in health, forms the basis of such conclusions. Numerous investigations, carried on by different persons, have shown that a well-nourished, healthy, adult man passes, on an average, from 25 to 40 grms. of urea in twenty-four hours, and from 1.0 to 1.66 grm. of urea in one hour.

Thus, calculating for the weight of the body, it follows that from 0.37 to 0.60 grm. are passed, on the average, in twenty-four hours, and from 0.015 to 0.035 grm. are passed in one hour for every kilogram of weight of the body.

The *absolute* quantity of urea passed by women, and, of course, also by children, is somewhat less. On the other hand, the *relative* quantity of urea passed by the latter, in proportion to the weight of the body, is greater than in adults. According to the computations of Uhle,\* children pass in twenty-four hours, for each kilogram of weight:

Children from 3 to 6 years of age, about 1.0 grm. of urea.

“ “ 8 “ 11 “ “ “ “ 0.8 “ “ “

“ “ 13 “ 16 “ “ “ “ 0.4 or 0.6 grm. of urea.

These normal averages are naturally somewhat variable in different people, and also in the same person at different times, according to the bodily constitution, variety of diet, and greater or less activity of metamorphosis. Moreover, they do not include the maximum and minimum quantities of urea in certain cases in perfectly healthy individuals.

Food, especially, has a decided and very great influence on

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\* Wiener medic. Wochenschr., 1859, 7 to 9.

the quantity of urea excreted. More urea is passed with a purely animal diet than with a mixed diet; and more with a mixed than with a vegetable diet; least of all is passed during complete abstinence from food.

The observations of O. von Franke \* give a very intelligible idea of the degree of this influence. He passed in twenty-four hours:

With a purely animal diet,	51	to	92	gram.	of	urea.
“ “ mixed	“	36	“	38	“	“
“ “ vegetable	“	24	“	28	“	“
“ “ non-nitrogenous	“			16	“	“

The importance which urea has for the physiologist and physician is that it forms an approximate measure of the metamorphosis of the protein compounds which exist in the body, and thus we find the quantity, not of the whole metamorphosis, but at least of a very important part of it.

Although the urea of the body comes originally from the protein substances, yet it does not spring directly from them. Various intermediate bodies are first formed by the metamorphosis, some of which yield urea more readily than others. (See page 4.) In certain processes of the metamorphosis, especially pathological ones, other substances instead of urea, as leucin and tyrosin, are formed. (See § 133.)

Whatever increases the metamorphosis of the protein substances, as a rule, increases the urea, and *vice versa*; therefore, the production of urea is in general rather greater during the waking hours than during sleep; it is increased by a rich, largely animal diet, and diminished by a sparing, or largely vegetable diet; it increases and diminishes with the degree of activity of the body and the mind. Therefore, the quantity of urea may be increased or diminished in perfectly healthy individuals by a variety of influences, which we will not consider any further here.

The quantity of urea passed with the urine in a given time does not depend alone upon the amount of urea produced, but also upon whether the urea formed in the body is completely

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\* Beiträge zur Kenntniss der Harnstoffausscheidung beim Menschen, Inaug. Abhandl., Würzburg, 1855.

separated or partially retained in the blood and parenchymatous fluids. Hence, the quantity of urea increases temporarily with the increase of the urinary secretion, and diminishes when it lessens.

The quantity of urea in disease depends on similar conditions.

A long-continued increase of the urea in the sick, always indicates increased conversion of the nitrogenous elements. A temporary increase of the urea, however, may depend on an increase of the urinary secretion, by which the urea collected in the body is quickly passed off, and does not necessarily indicate an increased production of urea.

A diminution of the quantity of urea may depend on:

- a. A diminution of the protein metamorphosis.
- b. A retention of the urea in the body (as in uræmia and dropsy).

The secretion of urea in all acute febrile diseases (pneumonia, typhoid fever, etc.) has naturally the following course:

At the commencement of the attack, and until the acme of the fever has been reached, the quantity of urea is generally increased, sometimes up to 50, 60, and even 80 grm. in twenty-four hours, and this in spite of a simultaneous low diet, and accompanying diminution of the quantity of urine. This increase of the urea, however, does not always keep pace with the increase of the bodily temperature.

Later, when the fever diminishes and the increase of metamorphosis has ceased, and while the continued disturbance of the appetite causes a diminished ingestion of food, the quantity of urea sinks below the normal.

During convalescence the quantity of urea gradually returns again to normal.

This regular course is naturally variously modified by individual circumstances.

In intermittent fevers the excretion of urea is markedly increased during the paroxysm of fever. This increase commences before the occurrence of the cold stage, which is important with respect to the theory of the fever.

In most *chronic* diseases, which are accompanied by a diminution of the tissue metamorphosis or of the nutrition, the quantity of urea sinks below the normal. During intercurrent exacerbations, hectic fever, etc., it is increased again.



The quantity is the least when diminished metamorphosis occurs at the same time with diminished action of the kidneys. For this reason, toward the fatal termination of many diseases, it is frequently very small (5 or 6 grm. daily).

In dropsical conditions it is frequently very much diminished, a portion of the urea being dissolved in the dropsical fluids and thus retained in the body. When, on the other hand, the secretion of urine is rendered abundant in such patients by the action of diuretics, or by a spontaneously increased activity of the kidneys, the secretion of urea will sometimes be considerably increased for a time, and then much more urea will be passed than is produced at the time. The excess of the excretion over the production arises from the supply stored up in the body.

If for a long time much less urea than normal is passed with the urine, we have reason to fear that uræmia may result from the retention of urea in the blood. Yet those cases are to be judged differently in which the urea is diminished in the urine or even wholly absent, because leucin and tyrosin are formed in its place, as in acute atrophy of the liver. (See § 133.)

Urine which contains a large quantity of carbonate of ammonium, which results from the decomposition of the urea, naturally contains relatively less urea than normal; the amount of urea, therefore, in strongly ammoniacal urine is no sure criterion of the quantity of urea produced. The method which must be followed in such cases in order to determine the urea is given on page 240.

The following examples will serve as explanations and proofs of the conditions given above:

*A. In health.*

A large number of estimations of urea, made according to Liebig's method, without correcting for the chloride of sodium, gave the following figures for strong, healthy men on good diet:

1.	In H.,	average quantity of urea per hour,	. . . . .	2.13 grm.
2.	" M.,	" " " " " "	. . . . .	1.47 "
3.	" J.,	" " " " " "	1st series of experiments, summer, 1852,	} 1.66 "
4.	" J.,	" " " " " "	2d series of experiments, Oct., 1853,	

The numbers given under 2 to 4 are the averages of a large

number (far more than a hundred) of observations ; consequently they represent pretty accurately the *average* production of urea in the individuals referred to at the time the experiments were conducted ; they are all, however, somewhat too high (probably about 10 per cent.), because the chloride of sodium was not precipitated from the urine.

On account of the large number of the above single observations they may also serve to indicate the amount of urea produced at different times of the day. The hourly quantity of urea amounted to :

			Morning.	Afternoon.	Night.
In M.,	.	.	1·7	1·58	1·2
" J., 1852,	.	.	1·68	1·71	1·61
" " 1853,	.	.	2·12	1·82	1·73

From this it appears that the amount of urea produced at different times of the day does not show much variation ; only during the night it was a little less than during the day in every series of experiments. Observations on the same individual at different times of the year (in J., in summer, 1852, and in October, 1853) likewise show a tolerably great uniformity.

To give an idea of the amount of the variations which the hourly secretion of urea in healthy persons may present, I will give the maximum and minimum of the hourly excretion of urea in each of the above series of experiments :

						Maximum.	Minimum.
1.	.	.	.	.	.	3·12	1·54
2.	.	.	.	.	.	2·45	0·88
3.	.	.	.	.	.	3·41	1·05
4.	.	.	.	.	.	2·82	0·89

#### B. *In disease.*

*In Typhoid Fever.* During the height of the disease the daily quantity of urea varied between 40 and 55 grm. As the fever diminished, it gradually fell to 20 grm., and during convalescence gradually rose again to the normal. In a case of typhoid which terminated fatally, the quantity of urea during the height of the fever amounted to 35, 40, and 50 grm ; it fell gradually as the disease approached a fatal issue to 25, 20, 10, and during the last twenty-four hours before death amounted to only 5 grm.

*In Pneumonia.* During the height of the fever the quantity

of urea increased to 50, 60, and even 70 grm., falling as the fever diminished to 25 and 20, and rising again during convalescence.

In a case of disease of the heart with dropsy the daily quantity of urea was for some time below the normal, 20, 25, and 28 grm. As the amount of urine was increased by diuretics, the quantity of urea also daily increased to 50 or 60 grm., but it fell again as the diuresis ceased. This state of things was several times repeated.

In a patient with rigid arteries and emphysema of the lungs, and who also suffered from an intercurrent attack of acute bronchitis with oedema of the lungs, the quantity of urea was generally small, below 30 grm. With the occurrence of uræmic symptoms the quantity fell to 12 and even 10 grm.; under the influence of diuretics it temporarily rose again to 25. Then came a new collapse with simultaneous diminution of the quantity of the urine and of the urea (to 11 grm.), and death.

During the last few years a large number of investigations respecting the quantity of urea secreted in different diseases have been published. They confirm in all main particulars the above general statements already published by me; which statements were based on very numerous observations made by me in the clinic at Giessen, in part before the publication of Liebig's method, at the instigation and with the assistance of my revered friend. A closer study here of the relation of the secretion of urea to particular diseases would lead us too far; that belongs to special pathology.\*

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\* Those who wish to pursue the subject further will find the most important literature as follows: Alfred Vogel (Henle and Pfeuffer Zeitschr., N. F. iv. 8). S. Moss (ibid. vii. 8). W. Brattler, Ein Beitrag zur Urologie, München, Palm, 1858. (All of these three works treat of the secretion of urea in different diseases.) W. Müller über Harnstoffabsonderung, etc., nach operativen Eingriffen (Wiss. Mittheil. d. Erlanger physik. med. Societät, 1858, Heft 1). R. Sander, Harnstoffausscheidung bei paralyt. Blödsinn (Virchow's Archiv, 1858, p. 160). F. S. Warneke, Harnstoffausscheidung im Typhoid (Bibl. for Laeger, xii., p. 330). Desgl. im Wechselfieber; Traube und Jochmann (Deutsche Klinik, 1855, Nro. 46). Sidney Ringer (Med. chirurg. transact., 1859, p. 360, *et seq.*, Desgl. in der Cholera; Fr. Lehmann (Inaug. Diss., Zürich, 1857). Traube (Berl. klin. Wochenschr., 1864, 17), Ueber vermehrte Harnstoffproduction in fieberhaften Krankheiten. E. Unruh (Virchow's Archiv, 1869, 48, p. 227, *et seq.*), Ueber die Stickstoffausscheidung bei fieberhaften Krankheiten.

## § 126. URIC ACID.\*

The quantitative estimation of uric acid is to be made according to the method described in § 73. In all cases in which the urine contains a sediment of uric acid or urates—and it is just in these cases that the quantitative estimation of uric acid has the most interest for the physician—we must naturally either employ the whole quantity of the urine in its estimation (in case it should not succeed the sediment is to be dissolved again completely by heat), or the urine must be filtered and the precipitated uric acid which remains on the filter, as well as that in solution in an aliquot part of the filtrate, must be determined, and then the whole quantity of uric acid contained in the urine calculated from these two together. But such an exact quantitative estimation of the uric acid is tolerably tedious and troublesome, and will rarely be undertaken, therefore, practically by physicians, who will usually content themselves with judging from the presence of a sediment of uric acid or urates in the urine how much the quantity of uric acid in it exceeds the normal amount. Such a conclusion, however, is not reliable; a sediment of urates frequently occurs without the quantity of separated uric acid appearing absolutely (that is, in a given time) increased. (See § 107.)

When we have determined the quantity of uric acid in the urine, the next thing naturally is to ascertain whether the quantity found is normal, or greater or less than normal. For this purpose it is necessary to know the average daily or hourly quantity of uric acid secreted by healthy people. Numerous investigations, especially by Lehmann, Neubauer, and chiefly by Ranke, have furnished tolerably accurate information on this point.

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\* H. Ranke, Beob. und Versuche über die Ausscheidung der Harnsäure beim Menschen, etc., München, Kaiser, 1858. B. J. Stokvis, Bijdragen tot de physiol. van het acid. uricum, Ned. Tijdschr., 1859 (Schmidt's Jahrb., Bd. 109, p. 3). Zabelin, Ueber die Umwandlung der Harnsäure im Thierkörper, Annal. d. Chem. u. Pharm., 1863, Suppl. ii., p. 326, *et seq.* Bartels Untersuchungen über die Ursachen einer gesteigerten Harnsäureausscheidung in Krankheiten (Deutsches Archiv f. klin. Med., i., p. 13, *et seq.*). B. Naunyn u. L. Reiss, Ueber Harnsäureausscheidung (Reichert's u. DuBois-Raymond's Archiv, 1869, Heft 3).

According to these observers the average quantity of uric acid which an adult individual (male as well as female) passes with the urine in twenty-four hours is from 0·3 to 0·8 gm. This average quantity, however, differs considerably in different individuals. Also in the same person at different times variations occur, which in many individuals are very considerable, in others less.

The nature of the food appears to exercise the chief influence over the quantity of the uric acid excreted. During fasting the quantity is diminished very much, it increases rapidly after eating, and almost as much after taking non-nitrogenous as animal food. (Ranke, W. Roberts.)

The relation of the quantity of uric acid to that of urea varies considerably (from 1 : 27 to 1 : 80, and indeed in a few cases from 1 : 300 and even more).

Lehmann passed an average of 1·18 gm. of uric acid in twenty-four hours, but considered that this was an abnormal amount.

According to Becquerel the daily average quantity amounts to 0·49 and 0·56 gm.

Neubauer found in a large number of observations on two healthy persons, that in one the average was 0·28, the maximum 0·61, the minimum 0·002. In the second the average for twenty-four hours was 0·49, the maximum = 0·67, minimum = 0·33.

Ranke, who has made numerous investigations, obtained as average numbers for twenty-four hours, in a long series of observations on himself, average 0·648, maximum 0·875, minimum 0·445. In other men, 0·225—0·654—0·556—0·78—average = 0·707, etc. In two women, the quantity in one was from 0·410 to 0·456, average = 0·429. In the second, from 0·458 to 0·565.

Regarding the effect of sickness, Ranke found that in intermittent fever an increased amount of uric acid was excreted during the attack. He found, moreover, that the uric acid was decidedly increased in leukæmia, a fact which was also observed by others; that it was sometimes diminished in diabetes mellitus, and (as shown by Garrod and Neubauer) always markedly diminished in chronic gout (where, according to Garrod, it is stored up in the blood). Large doses of sulphate of quinine, according to Ranke, diminished the excretion of uric acid.

Bartels found a decided increase of the uric acid, especially in proportion to the urea, in all of those febrile diseases which are accompanied with marked disturbances of the respiratory processes, and he therefore concludes that such an increase is the result of a relative respiratory insufficiency, that is, of an incomplete oxidation.

The causes and indications of an increase or diminution of the uric acid are, therefore, still somewhat obscure and hypothetical. Uric acid, like urea, is a product of the body, and in fact of the metamorphosis of the nitrogenous constituents. In so far it has the same indication as urea. But uric acid stands a step higher on the ladder of retrograde metamorphosis than urea; the latter may be formed from uric acid by oxidation. Therefore uric acid is often regarded as imperfectly oxidized urea, and it has been thought that the increase of the uric acid has always occurred at the expense of the urea, wherever, through the imperfect supply of oxygen, the decomposed nitrogenous elements of the body are incompletely oxidized before their removal from the system, and consequently in all diseases which are accompanied by disturbances of the respiration. This opinion, however, does not agree with the fact that perfectly healthy people also always pass a certain quantity of uric acid. Moreover, we find in those diseases in which an increase of the uric acid is most constantly observed—at the height of febrile diseases—that the excretion of urea is always increased as well as the uric acid. Uric acid, therefore, is surely something more than imperfect urea; but we must wait for future investigations to form further conclusions as to the true source of its formation and its actual significance in the economy.

Since the phenomena which occur in animals may serve to extend our knowledge of these relations, it is worthy of mention that in carnivora confined in cages and whose freedom to move about at will is, therefore, removed, the uric acid in the urine is increased. In herbivora uric acid is not found at all, but it appears in their urine when they are fasting, that is, when they live on their own flesh.

We have already spoken of the significance to the physician of uric acid deposited as a sediment within the body in § 107.

## § 127. FREE ACIDS.\*

The quantitative estimation of the free acids in the urine is easily and quickly made according to the method given in § 68. Only it must be commenced as soon as possible after the urine is passed, since the quantity of the free acids is readily changed by the occurrence of the acid or alkaline fermentation of the urine.

According to F. Soxhlet,† however, the titration of the degree of acidity of the urine by means of a solution of sodic hydrate yields a result which is accurate only within tolerably broad limits, since there is no soluble phosphate which has a neutral reaction, and since in titrating a point always occurs in which both acid and alkaline reactions are present at the same time.

Still, these limits of error are not so broad as to set aside the usefulness of such analyses, especially for practical purposes, when we content ourselves with only drawing conclusions from them which are not impaired by those unavoidable errors. (See § 124.)

Numerous observations of this kind which I conducted partly myself and partly had carried on under my guidance showed that a healthy man passed on an average daily about 2 or 4 gm. of acids with the urine, and in an hour about 0.10 to 0.20 gm. (calculated as oxalic acid). The hourly quantity varies not inconsiderably according to the time of day, and in four different persons on whom investigations were made it was uniformly greatest at night, least in the forenoon, and between the two during the afternoon.

The average hourly amount in the urine of the individual on whom the greatest number of investigations were made was in the night 0.19, forenoon 0.13, afternoon 0.15 gm.

The quantity of acids in the urine is undoubtedly diminished

\*Th. Eylandt, *De acidorum sumptor. vi in urinæ acorem*, Diss. inaug., Dorpat, 1854. J. Ch. Lehmann, *Bibl. for Laeger* xiii., p. 18 (*Schmidt's Jahrb.*, Bd. 108, p. 148). W. Roberts, *A contrib. to urology, embracing observations on the diurnal variations in the acidity of urine, chiefly in relation to food*, Manchester, 1850. Klüpfel (*Hoppe-Seyler, Medic. chem. Untersuchungen*, Heft 8, p. 412, *et seq.*). A. Sawicky (*Pflüger's Archiv*, 1872, v., p. 285, *et seq.*). C. Gaethgens, *Zur Frage der Ausscheidung freier Säure durch den Harn* (*Centralbl. f. d. medic. Wissensch.*, 1872, p. 833, *et seq.*).

† *Journ. f. prakt. Chemie*, 1872, vi.



by the use of caustic alkalies, carbonates or organic salts of the alkalies, indeed they may entirely disappear after large doses of these compounds and the acid reaction of the urine become alkaline, as in the formation of carbonate of ammonium by decomposition of the urea, as has been repeatedly mentioned.

On the other hand, the acidity of the urine is increased by the internal exhibition of the mineral acids.

*Example.* In a young man who had taken large quantities of mineral acids ( $\text{SO}_3$  and  $\text{ClH}$ ) for a long time on account of severe hæmoptysis, the daily average quantity of acid in the urine amounted to 5.4 grm. (an average of six days), and increased on one day to 7.5 grm. Gaethgens found also in dogs into whose stomachs he injected dilute  $\text{SO}_3$ , that the free acids of the urine were essentially increased thereby (from 13 to 72).

The very numerous and careful observations made by W. Roberts confirm the statements of B. Jones (see page 375, a) that during a period of time, from one to three hours after a meal, the secretion of acid by the urine diminishes both absolutely and in relation to the solid constituents of the urine. Not unfrequently, indeed, the urine at this time becomes temporarily alkaline. Mixed, purely vegetable, and purely animal diets have the same action. Roberts ascribes this result of taking food, as does also B. Jones, not to the secretion of acid gastric juice, but rather to the passage of alkaline salts, or of those which will become alkaline, from the food into the blood.

The greater or less amount of acid passed with the urine depends probably not only on the greater or less quantity taken, but also doubtless upon internal changes of metamorphosis, as already indicated in § 96, but not yet proved with certainty.

According to Klüpfel, the free acid of the urine is very much increased by great muscular activity. Sawicky, however, was unable to confirm Klüpfel's statements. According to his experience, the quantity and quality of the food had more influence on the degree of acidity of the urine than rest or work.

Numerous estimations of the quantity of acid in sick people have shown that in most diseases, acute as well as chronic, the acid is diminished and almost never increased, except in those cases in which large quantities of mineral acids have been taken. Yet we find during the height of febrile diseases, especially in pneumonia, acute rheumatism, etc., that the percentage

of free acid in the urine is not rarely increased, so that it appears more acid than in health; this evidently depends on the diminished quantity of the urine in such cases and its consequent greater concentration. The diminution of the quantity of acid in the urine of the sick doubtless chiefly depends on the diminished ingestion of food; perhaps, also, it is due in part to a diminution of the muscular metamorphosis in the sick (see page 376, b). The investigations which have been made thus far, do not allow of more special conclusions.

*Examples—Male:*

In a patient with pneumonia, the quantity of acid gradually increased from 0 to 1.50. The average of eight days amounted to 0.5.

In another patient with pneumonia, who died, the daily quantity varied between 0.9 and 3.0. The average of four days was 1.9.

In a case of gastric fever, the quantity varied between 0.6 and 1.6. The average of four days was 1.1.

In a case of acute rheumatism, the quantity for several days was 0.7 and 1.

In a case of chronic bronchial catarrh, the quantity varied during eleven days between 0 and 0.8. Average = 0.5.

*Female:*

In a girl with scrofulous glandular swellings it was from 1.6 to 2.4. The average of four days was 2.0.

In a woman thirty years of age, suffering from spinal irritation, from 0 to 0.8. Average of five days = 0.7.

In a woman seventy years old, suffering from ascites, the result of hepatic disease, from 0 to 3.1. Average of eighteen days = 1.41, etc.

§ 128. AMMONIA.\*

The methods of determining quantitatively the ammonia contained in the urine have been already described in § 77 and § 78.

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\* C. Neubauer, Journ. f. prakt. Chemie, lxiv., p. 177 and 278. W. Heintz and H. Bamberger, Würzburger medic. Wochenschr., Bd. 2, Heft 2 and 3. L. Thiry, Zeitschr. f. rat. Medic., 1863, p. 106, *et seq.* A. Duchek, Wochenbl. d. Zeitschr. d. k. k. Gesellsch. d. Aerzte zu Wien., 1864, Nr. 51. R. Koppe, Ueber Ammoniakausscheidung durch die Nieren (Petersburger med. Zeitschr. xiv. 2, 1868).

It appears from the investigations of Boussaingault, Heintz, and Neubauer, that human urine always contains a small quantity of ammonia. According to many experiments made by Neubauer on different individuals, the average quantity passed by healthy adult males in twenty-four hours was about 0·7 grm.; the quantity, however, may fall to 0·3, and rise to over 1 gram. Koppe also found in normal urine from 0·42 to 0·45 of ammonia per thousand parts; in women somewhat less. The absolute quantity in men amounted to 0·8 grm.; in women, to only 0·5 or 0·6 grm., in twenty-four hours.

Since only a few experiments have thus far been made on this subject, especially on the urine of sick people, the question as to what importance the increase or diminution of ammonia in the urine has for the physician can at present be answered only very insufficiently and hypothetically.

Duchek found ammonia always in the freshly passed urine of patients suffering from various febrile diseases and in not inconsiderable quantity, though it did not essentially exceed the quantities given above as observed in the urine of healthy people. The quantity of ammonia contained in the urine, moreover, appeared to him to increase with the aggravation of the symptoms of the disease, and to decrease as convalescence occurred. Koppe found the excretion of ammonia was increased in infectious diseases (1·3 to 1·5 grm. in twenty-four hours), and in the florescent stage of typhus, where it is increased with the temperature of the body.

The following considerations may serve as a hint, and at the same time as an incentive to further investigations:

The ammonia in the urine is evidently derived from two quite different sources:

1. It is derived from the food, from the drink, and from the respired air which contains more or less ammonia. Still, generally speaking, the amount of ammonia in these ingesta is but small, and consequently the quantity removed from the system by the urine is inconsiderable as a rule, less than  $\frac{1}{2}$  grm. in twenty-four hours. Under certain circumstances an unusually large quantity of ammonia may be taken into the system from without in health, as when we remain in an atmosphere filled with tobacco smoke, or eat certain food which contains much ammonia, such as radishes, etc.; in the sick,

when preparations of ammonia are given as medicines, such as the carbonate or chloride of ammonium, etc. Neubauer has shown that the greatest part of the chloride of ammonium ingested is eliminated again by the urine. In all cases in which the daily quantity of ammonia in the urine exceeds 1 grm. the physician should ascertain whether the excess depends upon one or several of these causes.

2. Without doubt ammonia may also be produced within the body by pathological processes. We know with certainty that urea may be decomposed into carbonate of ammonium, and one of the theories of uræmia is founded upon this dangerous process, that the urea retained in the system undergoes this change into carbonate of ammonium. The facility with which ammonia develops from all nitrogenous animal compounds, especially from the blood, the so-called extractive matters, etc., outside of the body, when a slight degree of decomposition has set in, allows us to conclude that in the pathological processes which we call putrid and septic, conditions of decomposition, such a development of ammonia has already taken place within the living body. Therefore, the detection of an increased separation of ammonia from the system is of great weight in the diagnosis of such conditions of disease (ammonæmia). The ammonia may be separated not only by the urine, but also in other ways, as by the intestine and the lungs, but its quantitative estimation in the urine is at present our simplest and surest guide.

Great care, however, is necessary in the investigation of all such cases, since under these circumstances the urea of the urine has a great tendency to decompose (which, as Neubauer has shown, does not happen in normal urine), and it is, therefore, very difficult to determine how much of the ammonia present in the urine was present when it was first secreted, and how much has been formed by the subsequent decomposition of urea in the bladder or outside of the body. In order to avoid this source of error as much as possible, I would advise in all such cases :

1. To subject the urine to examination as soon as possible after its secretion by the kidneys, by introducing a catheter to draw off all of the urine present in the bladder, and then to subject that which drops from the catheter subsequently to an examination.

2. To free this urine from coloring matter, extractive matter, mucus, etc, by the addition of acetate and basic acetate of lead solutions, as described on page 308, so as to guard against further decomposition as much as possible.

Sometimes the urine contains sulphide of ammonium. Betz considers that in such cases it comes from the intestine, from which it is absorbed into the blood, and there causes dangerous symptoms of disease (hydrothion-ammonæmia). (See page 143.) The acceptance of this origin, however, requires further proof, since the intestine, even in perfectly healthy persons, very often contains sulphuretted hydrogen without showing any results of the action of this poisonous gas on the blood.

### § 129. CHLORINE AND CHLORIDE OF SODIUM.\*

For the methods of estimating the amount of chlorine and common salt in the urine, see § 66.

It is immaterial whether the result of the estimation is reckoned as chlorine or chloride of sodium, although it is certain that in many cases all of the chlorine in the urine is not combined with sodium. Therefore care must be taken not to confound the figures indicating chlorine with those which indicate chloride of sodium, which occasionally has happened, and has led to error, since many writers calculate their results as chlorine, and others as chloride of sodium.

The starting point for deciding whether the elimination of chlorine with the urine is increased or diminished is the knowledge of the average daily elimination of chlorine in health. Hegar has reported a series of very careful examinations of the daily and hourly elimination of chlorine with the urine in seven young healthy men. The average daily amount in the urine varied with the individual, between 7.4 and 13.9 gm. Therefore the average daily amount of chlorine passed with the urine by an adult man is about 10 gm. (=16.5 gm. NaCl), or hourly about 0.44 gm. Cl (0.73 NaCl). These figures are, however,

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\* Alfr. Hegar, Ueber die Ausscheidung der Chlorverbindungen durch den Harn. Giessen, 1852. F. Howitz, Hospitals Meddelelser : andere Roekke, Bd. 1, p. 64, *et seq.* ; Schmidt's Jahrb., Bd. 95, p. 282, *et seq.* E. Ph. Hinkelbein, Ueber den Uebergang des Chlornatriums in den Harn., Inaug. Diss., Marburg, 1859.

probably somewhat too high, since the individuals taken for the examination were mostly students who were strong, ate food with much salt, and drank much. A somewhat lower figure would be more nearly correct for the majority of adults, about 6–8 gm. Cl (=10–13 gm. NaCl) daily, and 0.25–0.33 gm. Cl (=0.41–0.54 gm. NaCl) hourly. In women and children the amount of chlorine eliminated is still less.

Bischoff found as the mean daily amount of chlorine in the urine of a well-nourished adult man, 8.7 gm., of a woman 43 years old, 5.5 gm., of a girl 18 years old, 4.5 gm., of a boy 16 years old, 5.3 gm., and in that of a boy of 3 years, 0.8 gm. Becquerel found only 0.66 gm. Cl in the ignited residue of the daily urine of a healthy person, an estimate, like all others obtained in the same way, naturally of no value.

But very considerable variations in the amount of chlorine eliminated daily and hourly may occur, not only in different individuals, but also in the same person under conditions of health. This follows partly a certain rule. Thus, in all healthy persons examined, the maximum chlorine elimination occurs in the afternoon, and the minimum at night.

Hegar found as the mean hourly elimination in eight individuals: afternoon, 0.57; night, 0.28; forenoon, 0.48 gm. The same author found in the same individual variations in the hourly elimination from 0.20 to 1.32 gm., so that the hourly maximum exceeded the minimum more than sixfold.

The following are doubtless the causes which produce an increase or a diminution in the chlorine elimination in healthy persons:

1. The taking into the organism of a greater or less amount of chlorine, especially of common salt, which we eat with our food, has without doubt the greatest influence. Persons who eat much salt with their food have a greater average elimination of chlorine, and a temporarily increased ingestion of chlorine results, as a rule, in a temporary increase in the elimination. That the greatest hourly chlorine elimination in all persons examined here occurs during the afternoon and evening hours, depends, without doubt, chiefly upon the fact that all of these persons eat the greatest amount of salt with their principal meal at noon, a part being eliminated soon after its

passage into the blood. But also direct experience shows that after the increased ingestion of chlorine there is an increased elimination with the urine and *vice versa*.

Falck eliminated with the urine daily : 1. When eating food well salted—on the first day, 6·0 grm. Cl ; on the second, 7·8 grm ; on the sixth day, 10·3 grm. 2. When eating food not salted—on the first day, 2·5 grm. Cl ; on the second, 1·6 grm., and on the third day, 0·9 grm.

Several persons here took, for the purpose of experiment, common salt in non-purgative doses. In all cases the hourly elimination with the urine was increased ; it rose from 0·4 grm. to 1·0, and even to 1·8 grm. In some the chlorine which was absorbed into the blood was again separated from it in large amount and quickly, but in others in smaller quantity and more slowly.

In experiments which Stokvis undertook, the amount of chlorine in the urine diminished rapidly with the diminution of the amount ingested, and rose again gradually when more salt was eaten.

2. But the amount of chlorine eliminated with the urine depends not only upon the amount ingested, but may be increased or diminished by other circumstances, and even by conditions which lie within the organism itself. In all of the persons examined by Hegar, the hourly elimination in the forenoon hours (0·48 grm.) was much greater than during the night (0·28 grm.), although one of these persons was accustomed to eat a meal of well-salted food in the evening, and then take nothing but a glass of water until the next noon, and the others also ate food rich in salt in the evening, but in the morning only food containing but little salt (coffee and rolls) ; so that in all of these cases there must have been other causes which diminished the power of the kidneys to eliminate chlorine during the night and increased it during the forenoon. Without doubt these causes are, on the one hand, the physical and mental quiet during sleep, and on the other, the greater activity of metamorphosis during the morning, causes which, as has been already shown, exert an analogous influence upon the amount of the urine and of the urea. An exceptional case, agreeing with this theory, occurred in one of the persons examined by Hegar, who was accustomed to strenuous mental exertion during the greater



part of the night, in whom the mean hourly amount of chlorine in the night urine (0.47 gm.) exceeded that in the morning urine (0.44 gm.). I have also frequently observed myself that the elimination of chlorine was temporarily considerably increased by an increase of physical and mental labor. Agreeing with this also, the observation has been made that drinking a large amount of water, which excites the activity of the kidney and increases not only the amount of urine but also the amount of urea eliminated, as a rule, causes also a temporary increase in the amount of chlorine eliminated, followed usually by a diminution or lessening of the activity.

*Example.* H. drank in the evening four glasses of water. The hourly elimination of chlorine, which averaged in this person only 0.13 gm. during the night, rose during the next hours to 0.60 gm., then fell to 0.12, and later to 0.10 gm., and rose again in the morning without anything more having been eaten by increased metamorphosis (riding) to 0.51 gm.

H. V. drank in the afternoon four glasses of water. The hourly chlorine elimination thereupon increased during the evening hours to 1.89 gm., and averaged during the night 0.57 gm. (instead of 0.38 gm.). In the morning two glasses more of water were taken, in spite of which the amount remained during the whole day below the normal (0.42 gm.), and even fell during the night to 0.014 gm. (!), in the morning rose again somewhat (to 0.22 gm.), but then fell once more (to 0.18 gm.), notwithstanding that bread and butter with a large amount of salt was eaten.

From these results it follows without doubt that the amount of chlorine eliminated depends not only upon the amount ingested, but that it is influenced much more by other causes, especially those which act generally upon the activity of the kidneys, producing an increase or diminution in the amount of urine. But it is very difficult to estimate accurately the influence of these conditions upon the elimination of chlorine generally, and particularly in any given case. In order to do this we must give the individual chosen for the investigation a diet absolutely free from chlorine, which would, however, certainly disturb the purity and usefulness of the results obtained, or we must take the greatest care to estimate accurately the amount of chlorine in all of the food taken while the investigation lasts,

as has been done by Barral in some cases in his careful investigations.\*

We will now turn to the consideration of the elimination of chlorine in *disease*. In this subject I have a very large number of experiments, part of which I have performed myself and part have superintended. The results are chiefly as follows :

1. In all acute febrile diseases the amount of chlorine eliminated with the urine diminishes rapidly, frequently sinking to the minimum, almost to complete disappearance, so that sometimes it amounts to scarcely the one-hundredth part of the normal. With commencing recovery it increases, and during convalescence sometimes exceeds the normal. Its curve usually runs parallel with that of the amount of urine, for the most part, however, in the opposite direction to that of the specific gravity and the coloring matters, and at the beginning to that of the urea, but during convalescence frequently parallel with that of the urea.

*Example.* In the case of a man with severe pleuropneumonia the chlorine diminished rapidly, amounting on the third day after the commencement of the disease to 0·6 grm. daily, on the next day to 0·3 grm., and on the following to almost 0, from which time it increased continuously with the decrease of the disease and the increase of the appetite, with tolerable regularity, until the normal was reached (0·4—1·8—2·6—5·5—9·0 grm.). From this time the curve became irregular, and sometimes exceeded the normal (10·7—13·5—9·7—11·9—15·9—10·8 grm.).

In a typhoid-fever patient it fell quickly to a minimum, remaining for several days almost at 0. Then it increased with advancing recovery gradually, with variations, until it reached the normal.

In a woman with acute rheumatism and pericarditis it fell during the acme to 1·0 grm., and rose gradually during convalescence to 6·3 grm.

In a young man with severe febrile bronchial catarrh it fell quickly to 0·8 grm., and then rose during five days to 10·6 grm.

In an older man also with febrile bronchial catarrh it fell to

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\* J. A. Barral, *Statique chimique des animaux, appliquée spécialement à la question du sel*, Paris, 1850.

1.1 grm., but then rose during convalescence, when an abundant amount of nourishment was taken, to the enormous height of 20.5 grm.

In a man with exudative pleurisy it diminished to a mere trace, and then rose again with some variations, without, however, reaching a very high figure (3.0—3.2—4.8—1.6—4.0—4.5—4.9—4.6 grm.).

The cause of this very great diminution in the amount of chlorine eliminated in all acute diseases is, without doubt, chiefly the diminution of the appetite and the meagre diet, poor in salt, taken by such patients; the separation of chlorine from the blood by other channels (watery diarrhoea, serous exudations) sometimes causes it. By all of these conditions the amount of chlorine in the blood is certainly diminished, and since, as we see in health, the *excess* of chlorine in the blood is preferably separated by the kidneys, it is very probable that the amount of chlorine in the urine is diminished.

The amount of chlorine eliminated with the urine is also directly dependent upon the amount of urine, and the circumstance, that this is always considerably diminished in all acute febrile diseases, probably diminishes also the amount of chlorine compounds eliminated.

Since the above statements concerning the elimination of chlorine with the urine in disease, based upon numerous investigations of my own, were published, several works upon this subject have appeared, such as that of Howitz and Hinkelbein mentioned above, and those of Alfr. Vogel, Moos, and Brattler mentioned in connection with urea, which also dealt with the elimination of chlorine with the urine. They confirm, in the main, the above statements, and especially that it is not in single forms of disease only that the diminution in the amount of chlorine is observed, for example, in pneumonia, but in the *whole* class of the above-mentioned diseases, so that the diminution or the disappearance of the chlorine compounds from the urine cannot, as some state, be used for the purpose of making a differential diagnosis, of pneumonia, for example. My results have been confirmed by those of Howitz and Fel. Hoppe\* in this respect also—that this diminution of the chlo-

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\* Deutsche Klinik, 1858, No. 52.

rine is particularly dependent upon the diminished ingestion of chlorine (naturally together with the other causes mentioned above).

An exception to this rule, which otherwise applies to all acute febrile diseases, is *intermittent fever*. In this disease the elimination of chlorine with the urine appears usually to be increased, in many cases to a very great extent, during the paroxysm, sometimes shortly after it, and more rarely shortly before it.

*Example.* W. K. suffered with tertiary intermittent. Shortly before the attack the hourly amount of NaCl eliminated with the urine was 0.07 gm., during the paroxysm it rose to 0.62 gm., then fell to 0.39 gm., and in the following interval to 0.17 gm. During the next paroxysm it increased again to 0.93 gm. and fell again during the interval to 0.04 gm.

A. S. Tertiary intermittent. The hourly amount of chloride of sodium was 0.05 gm. before the paroxysm, rose to 2.5 gm. (!) during it, fell again to 0.12, and then rose again gradually to the normal, since there were no more attacks.

A. C. Tertiary intermittent. The hourly elimination of chloride of sodium amounted to 0.42 gm. before the attack, rose to 1.30 gm. during it, and then fell to 0.15 gm. It rose again toward the end of the interval, reached its maximum of 0.63 gm. shortly before the beginning of the fever, and then fell to 0.08 gm.

The same rule naturally applies to women. Auguste S. suffered from tertiary intermittent. The hourly elimination of chloride of sodium amounted to 0.15 gm. shortly before the attack, during the paroxysm it reached the enormous height of 4.12 gm., and fell again after the paroxysm to 0.06 gm.

The average daily elimination of chlorine in intermittent fever is, however, somewhat less than normal, but it does not for any length of time undergo the considerable diminution which is observed in other acute diseases; this is due to the fact that intermittent-fever patients frequently have during the interval a good appetite and eat food with the ordinary amount of salt. The increased elimination during the paroxysm is probably due to the increased blood pressure in the Malpighian bodies of the kidneys during the chilly stage. A diminished separation of chloride of sodium from the blood, which has be-

come poor in salt, then naturally follows the increased elimination.

2. In *chronic diseases* the elimination of chlorine is subject to great variation. As a rule it is diminished, corresponding to the diminished metamorphosis and ingestion of food by such patients, but in individual cases it is, on the contrary, increased. Some groups of diseases belonging under this head are of special interest in this respect and deserve a more accurate consideration.

The chlorine appears to be increased in diabetes insipidus, sometimes temporarily, sometimes for a long time together with an increase in the amount of urine and of the solid constituents generally. In one case of this kind I found the elimination of chlorine with the urine increased for a long time, so much that on one day the enormous amount of 29 gm. was reached.

In dropsy at the time when the elimination of urine is suppressed, a part of the salt eaten is held back in the body: it transudes with the dropsical fluid into the tissues. With the appearance of diuresis the elimination of chlorine increases together with the amount of urine, and then sometimes reaches an enormous amount. Thus, in one case, such a patient passed on three successive days 33 (= 55 gm. NaCl), 28, and 21 gm. of chlorine, and in another the elimination of chlorine rose within twenty-four hours, on account of the influence of a decoction of digitalis, from 4 gm. to 27, without the ingestion of chlorine being in the slightest increased. The same process which is injurious in the first class of cases, diabetes, by withdrawing substances from the economy which are necessary, is beneficial in the latter class, dropsy, by separating the superfluous material. While a certain amount of chloride of sodium appears to be necessary to the organism, partly for many secretions, partly for the purposes of intermediate metamorphosis, secretion of the gastric juice, the bile, and for the formation of many tissues (especially cartilage?), nevertheless an excess of it may be injurious, namely, by preventing the formation of the blood and by displacing albumen.\*

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\* Concerning this last property I have already given a detailed treatise in the *Handbuch der spec. Pathologie und Therapie*, published under R. Virchow's revision, Bd. 1, page 404, *et seq.*, and I must here refer to that treatise.

A quantitative estimation of the amount of chlorine eliminated with the urine may in the present state of our knowledge give the practising physician information upon the following points:

In all acute diseases a progressive diminution of the chlorine shows an increase, and progressive increase of the chlorine, a diminution of the disease. If the chlorine falls to a minimum (below 0.5 gm. daily), the conclusion that there is a considerable intensity of the disease, a complete failure of the appetite, or, under certain circumstances, a previous abundant watery diarrhoea or moderate serous exudation is warranted. If the chlorine increases again in the urine we may, from its amount, draw a tolerably accurate inference as to the condition of the appetite and digestion of the patient. In all of these cases a very approximate estimation of the amount of chlorine is usually sufficient, and an error of 50 or 60 per cent. is of no importance, especially in cases where the elimination of chlorine is very slight.

In chronic diseases the amount of chlorine is of importance to the physician, since it is a tolerably accurate measure of the digestive power of the patient. An abundant amount of chlorine (6–10 gm. daily) permits us to infer that digestion is good, a small amount (below 5 gm.) shows a weak digestion, providing that no large amount of chlorine is separated by other channels, as, for example, by abundant watery dejections, or any other moderate exudation, or that the diet of the patient has unintentionally been so chosen that a very small amount of chlorine is ingested. A very much increased chlorine elimination (more than 15–20 gm.) indicates diabetes insipidus, provided that there has not been an increased ingestion with food or drugs. Only in hydræmia and dropsy is it a good sign. The consideration of the other urinary constituents serves often to strengthen or to modify the inferences drawn from the amount of chlorine alone.

### § 130. SULPHURIC ACID.\*

The methods for determining quantitatively the amount of

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\* G. Gruner, *Die Ausscheidung der Schwefelsäure durch den Harn*, Giessen, 1852. Wald. Clare, *Experimenta de excretionem acidi sulfurici per urinam*, Dorpat, 1854. P. Sick, *Vers. über die Abhängigkeit des Schwefelsäuregehalts des Urines von der Schwefelsäurezufuhr*, Inaug. Abhdlg., Tübingen, 1859.

sulphuric acid in the urine have been already described in § 69. Both the gravimetric and the volumetric methods, when they are carefully performed, give very accurate results. If it is desired to obtain the result very quickly, the volumetric method should be used without boiling, since this operation is usually inconvenient for the physician. But the result is then less accurate, and the error may reach 10 per cent. An approximate estimation, which will not accurately give the amount of sulphuric acid contained in the urine, but will only show whether it exceeds or falls below a certain point, may be performed still more quickly, and is sufficient for most purposes of the physician. An example will explain the principle and the performance.

We will take the case in which the physician wishes to know whether the elimination of sulphuric acid with the urine of a patient is *considerably* increased or diminished. The average normal amount of sulphuric acid in the urine daily is about 2 gm. The patient whose urine is to be examined has passed 2,000 cc. in the twenty-four hours. If this contains the normal amount of 2 gm., then 100 cc. of it, which are taken for analysis, will contain 0.10 gm. of  $\text{SO}_3$ . To this 100 cc. is now added, after it has been acidulated, an amount of chloride of barium equivalent to 0.05 gm.  $\text{SO}_3$ , and filtered. If the filtrate is not rendered turbid by more chloride of barium, we know that the patient is secreting less than 1 gm. of  $\text{SO}_3$  in twenty-four hours, and, therefore, that the elimination of sulphuric acid is considerably diminished in his case. If the filtrate is rendered turbid, however, by the addition of more chloride of barium, enough more must be added to correspond to 0.05 gm. of  $\text{SO}_3$ . If then, after filtering, a turbidity is caused by the addition of chloride of barium, the amount of sulphuric acid in the urine exceeds the normal. Such approximate estimations, which are entirely sufficient for many practical purposes, may be performed in a few minutes, and in a clinic, directly at the bedside. Even in cases in which a more accurate estimation is desirable, they may profitably be performed as a preliminary to a more careful analysis.

The average amount of sulphuric acid eliminated with the urine in *health* has been established with tolerable certainty by different observations in various places. Thus Gruner, who



made his investigations in Giessen upon seven young men, found as the average of the daily elimination 2.094 gm. Of these seven persons the average in those who passed the least sulphuric acid was 1.509 gm., and in those who passed the most was 2.485 gm. These figures, reckoned for 100 kilogr. weight of the person, give as the average 3.19, minimum 0.85, maximum 3.73; reckoned for 100 ctm. height of the person, give as the average 1.18, minimum 1.04, maximum 1.35. Clare found that the average daily elimination for 15 days in a young man in Dorpat was 2.288 gm., minimum 1.858, maximum 2.973. Neubauer found in one of two men living in Wiesbaden as the daily average (for 17 days) 2.48 gm., minimum 1.90, maximum 3.21 gm. In the other the average for 22 days was 2.27, minimum 1.70, maximum 3.20 gm. Sick found as the average in his own case 2.46 gm. Weidner, 2.1 gm. Therefore the average daily elimination of sulphuric acid with the urine in healthy, well-nourished men varies between 1.50 and 2.50 gm. Gruner and I have made direct experiments upon the hourly elimination of sulphuric acid in health and upon its variations. From these it follows that the general hourly average is about 0.090 gm., that in the afternoon is 0.108 gm., in the night 0.070 gm., and in the forenoon 0.063 gm. From this the general rule follows that the elimination of sulphuric acid is most abundant a few hours after the principal meal, and then falls constantly until the time of the principal meal on the following day, after which it begins to rise again. But with different individuals the elimination of the sulphuric acid taken into the body with the food takes place with more or less energy, more quickly or more slowly, so that the sulphuric acid curve becomes more or less steep. But the variations in the hourly elimination of sulphuric acid are very considerable in the same person. Thus one person evacuated in one hour a maximum of 0.165 gm., and at another time in two hours an amount so small that it could not be estimated, at the most, therefore, a couple of milligrams. In another person the hourly maximum was 0.317 gm., and immediately afterward only 0.016 gm. were passed per hour.

As to the *causes* which influence an increase or diminution of the sulphuric acid elimination in health, the investigations have been quite numerous.

It follows from the above reported rate of the hourly elimination of sulphuric acid, that it depends to an important extent upon the amount of sulphuric acid or other sulphur compound, which is converted within the organism into sulphuric acid, taken into the body with the food. But it is also proven by numerous experiments, that sulphur compounds which are taken into the body in other ways, as for example as drugs, cause an increase of the  $\text{SO}_2$  elimination. The investigations hitherto made in this respect teach us the following points:

1. The elimination of sulphuric acid is increased by the ingestion of sulphuric acid, sulphates, and other sulphur compounds whose sulphur may be oxidized within the body to sulphuric acid.

*Examples.* In the case of a patient in my clinic, who took  $\text{SO}_2$  for a long time on account of hæmoptysis, the daily sulphuric acid elimination was increased from 1.2 grm. to 3.0 and even 3.28 grm.

Also in a case of  $\text{SO}_2$  poisoning, the amount of it in the urine during the first 24 hours was much increased. (Mannkopff.)

In several experiments the hourly elimination of sulphuric acid was much increased by taking sulphate of sodium. Thus in one it was increased from 0.049 grm. to 0.122—0.176—0.145 and 0.220 grm., and in another from 0.041 to 0.138—0.122 and 0.164 grm. This increase continued sometimes for a longer and sometimes for a shorter time, that is, the sulphuric acid ingested was separated from the body in some cases quickly and in some more slowly. (Gruner.)

According to Krause\* the internal use of sulphur increases the amount of sulphuric acid in the urine; it is also increased, according to the experiments of Boecker and Clare, after large doses of sulphur auratum antimonii (golden sulphur).

It follows from the experiments of Sick that small doses of sulphate of sodium taken internally are completely absorbed and eliminated with the urine, while only a part of large doses appears again in the urine—which would be expected on account of the cathartic action of large doses of Glauber's salt (sulphate of sodium).

C. Gaethgens† found also that in dogs after the injection of

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\* A. Krause, *De transitu sulfuris in urinam*, Dorpat, 1853.

† *Centralbl. f. d. medic. Wissensch.*, 1872, p. 833, *et seq.*

dilute sulphuric acid into the stomach its amount in the urine was considerably increased (from 2·7 to 7·1 grm.).

2. The sulphuric acid elimination is very decidedly increased after the abundant ingestion of meat, which is probably due to the separation during digestion of the sulphur which is in combination with the protein substances in the meat, and its gradual oxidation in the blood to sulphuric acid, in which form it is eliminated with the urine. This increase of the  $\text{SO}_3$  in the urine after eating meat sometimes appears quickly, a few hours after eating, and sometimes not for a long time, 12–24 hours, a difference which is probably due to the greater or less rapidity of digestion. On the other hand, the sulphuric acid elimination is diminished by a predominance of vegetable food.

*Examples.* A person who had eaten in the evening a very hearty supper consisting chiefly of meat, evacuated from 12 o'clock at midnight to 9 o'clock in the morning 0·50 grm. of  $\text{SO}_3$  per hour instead of 0·10 grm., and during the next 24 hours it amounted to the enormous sum of 7·3 grm. (!) instead of the daily average of 2·02 grm.

Several persons, whose metamorphosis I investigated, constantly eliminated more  $\text{SO}_3$  when they had eaten meat on the previous evening, and less when they had eaten no meat but only bread and butter, rice, and similar substances.

Very instructive in this respect is a series of experiments which Clare made upon himself. During three days he took only a meat diet, and in this time evacuated, on the first day 2·094, on the second 5·130, and on the third 3·868 grm. of  $\text{SO}_3$ . Then for two days he ate ordinary food and evacuated on the first day 3·592, and on the second 2·262 grm. of  $\text{SO}_3$ . On the three following days he lived upon an exclusively vegetable diet, when the amount of  $\text{SO}_3$  was on the first day 2·262, on the second 1·394, and on the third 1·022 grm.; on the two following days with ordinary diet it was 1·979 and 2·859 grm. It is plainly seen here that the increase of the  $\text{SO}_3$  caused by the meat diet first appeared on the second day, but extended over into the first day of the ordinary diet; in like manner the diminution of the  $\text{SO}_3$  caused by the vegetable diet first appeared on the second day and extended over into the first day of the ordinary diet. Therefore, in these cases the action appeared later than in those which were observed by me, probably on

account of individual predisposition, and for this reason probably another experiment of Clare, in which he ate on alternate days a meat and vegetable diet, gave no positive result.

Does the amount of sulphuric acid eliminated with the urine always depend entirely upon the amount ingested, or are there, as with common salt, cases in which the elimination of this substance is increased or diminished by other conditions, so that the system gives up a portion of its usual, fixed, normal amount of sulphur or sulphuric acid, whereby it becomes poorer in this constituent than usual, or, on the contrary, holds back a portion of the sulphuric acid obtained from without, and thereby becomes richer in this constituent than usual? This question cannot yet be answered with certainty. Gruner and Clare have endeavored to determine by experiments whether rest or strenuous exertion exerted any influence upon the  $\text{SO}_2$  elimination. None of their experiments gave a satisfactory result. Drinking a large amount of water, which decidedly increases the secretion of urea and chloride of sodium, has no marked influence upon that of sulphuric acid. But we are not yet warranted in concluding from these experiments that the  $\text{SO}_2$  elimination is not affected by such influences: it may have been very slight, or have been prevented in these experiments by opposing influences. The fact mentioned above, that the sulphates or sulphur constituents of meat which is eaten are eliminated rapidly by some persons and more slowly by others, renders it extremely probable that there exist still other considerations lying within the organism itself, which regulate the  $\text{SO}_2$  elimination, and that this power varies in different persons and in the same person under different circumstances. Also the experience often met with, that sulphates taken for a long time in digestible doses exert a decidedly different action, is to my mind a proof that under certain circumstances an amount of them greater than the normal may be retained within the organism. A definite answer to this question can only be obtained by either accurately estimating the amount of sulphur and sulphuric acid in the blood and other parts of the body under different circumstances, or by simultaneously accurately determining quantitatively the amount of sulphuric acid eliminated from the body and that taken into it. Both of these requirements are so difficult to fulfil, that this

question will probably remain unanswered for a long time to come.

As to the sulphuric acid elimination in *disease* I have made quite a number of investigations, without as yet having arrived at any very valuable result. In most acute febrile diseases I found the  $\text{SO}_2$  very much diminished, which was without doubt due to the scanty diet and the predominance of vegetable food in such cases.

*Examples.* A man suffering with buccal diphtheria with violent fever evacuated in the twenty-four hours only 0.5 gm. of  $\text{SO}_2$ . A patient with catarrhal fever 0.29 and 0.38 gm. One with pleurisy 0.63 gm. An exception occurred, however, in three cases of severe pneumonia, in which the sulphuric acid was partly slightly diminished and partly considerably increased. One of these patients, who was treated with large doses of digitalis, evacuated 2.4—3.1—2.9—5.7—4.3—1.8—1.1—1.6—2.7 gm. Of the other two, in whom the pneumonia rapidly proved fatal, one eliminated 2.9 and 1.4 gm., and the other on the day of death 4.4 gm.

A girl with severe rheumatic fever eliminated at the acme of the disease 0.8 gm. One with facial erysipelas passed 0.48 gm.

In chronic diseases also the sulphuric acid elimination was very slight in many cases, in others somewhat greater, but still considerably below the normal. In dropsy, at the time when, on account of diuresis, the chlorine elimination is so enormously increased, the sulphuric acid, as a rule, remains below the normal. In chronic diseases the  $\text{SO}_2$  was found to be increased almost only after the use of sulphuric acid or sulphates, and in diabetes where an abundant meat diet was eaten.

*Examples.* A patient with icterus passed 1.4 gm. of  $\text{SO}_2$ , and one with rheumatism of the neck 1.11 gm. A patient with emphysema of the lungs 1.2 gm., one with amenorrhœa 0.5 gm., a girl with leucorrhœa 0.7 gm., and a patient with habitual hypermenorrhœa 0.97–1.1 gm. A dropsical patient, after diuresis had commenced, passed in twenty-four hours 33 gm. of chlorine with the urine, but in the same time only 1 gm. of  $\text{SO}_2$ , and on the following day when he passed 28 gm. of chlorine only 0.5 gm. of  $\text{SO}_2$ . A patient who had taken  $\text{SO}_2$  eliminated in twenty-four hours over 3 gm., and one with diabetes insipidus up to 5.2 gm. of  $\text{SO}_2$ .

According to Bence Jones, in those diseases in which the muscular system is especially attacked, as in chorea, also in diseases of the brain, both functional, as in delirium, and organic, as in inflammation of the brain, the sulphates in the urine should be considerably increased. Heller claimed the same for inflammatory diseases, while, according to him, the  $\text{SO}_3$  should be diminished in chlorosis, the neuroses, and in chronic renal and spinal affections. The methods, however, which both of these investigators used were not sufficient to decide this difficult question. Single observations which Lehman and Gruner made are not favorable to that view. My own observations in those diseases have not been sufficiently numerous to enable me to draw any definite conclusions either for or against them; the three cases of pneumonia reported above appear at all events to favor the view that in many inflammatory diseases the  $\text{SO}_3$  increases.

The physician can, in the present state of our knowledge, draw the following conclusions from an increase or diminution of the sulphuric acid in the urine :

1. A considerable diminution of the  $\text{SO}_3$  indicates that the patient has eaten very little animal food, or only vegetable food ;

2. An habitual, abundant sulphuric acid elimination in connection with a large amount of urea, indicates a preponderance of animal food. A temporary and considerable increase allows us to conclude that sulphur, sulphuric acid, sulphates, or large quantities of meat have been eaten ;

3. Only in those cases of violent febrile diseases, where little or nothing is eaten, and in which the  $\text{SO}_3$  appears to be considerably increased, can the conclusion be drawn that this increased elimination is due to an increased decomposition of those constituents of the body.

### § 131. PHOSPHORIC ACID.\*

The most convenient and best method for estimating quanti-

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\* A. Winter, Beiträge zur Kenntniss der Urinabsonderung bei Gesunden, Giessen, 1852. F. Mosler, Beiträge zur Kenntniss der Urinabsonderung, Giessen, 1853. W. Brattler, Ein Beitrag zur Urologie, München, 1858. H. Krabbe, Ueber die Menge der Phosphorsäure im Harn, etc., Virchow's Archiv, 1857,

tatively the amount of phosphoric acid in the urine is the volumetric method with oxide of uranium, described in § 67.

Formerly ferric chloride was used for this purpose instead of the oxide of uranium, but it gives much less accurate results. The investigations mentioned above, and those reported in the following pages, were mostly performed with ferric chloride. Yet the results agree closely enough with those which were obtained by H. v. Haxthausen under my direction, and in which the oxide of uranium was used.

There are numerous series of investigations concerning the daily and hourly elimination of phosphoric acid in health. Breed found as the average amount in twenty-four hours in four individuals 3·7 grm.; Winter, in one person, 3·7, in a second, 4·2, and in a third, 5·2 grm.; in the same person at two different times, 2·4 and 3·7 grm.; Neubauer found in one individual 3·1 grm., in another only 1·6 grm.; Aubert found 2·8 grm.; v. Haxthausen found in a large series of investigations upon his own urine from 3·11 to 5·58 grm.; Riesell, 2·7 to 2·9 grm. We may, therefore, consider about 3·5 grm. as the average amount of phosphoric acid eliminated in twenty-four hours by a male adult, although it must be observed that the individual average may vary very considerably from this figure. The average hourly amount is, therefore, about 0·15 grm. Winter has calculated the amount of  $\text{PO}_5$  for the weight and height of the body, and found that the average hourly amount for 100 kilogr. is 0·27 grm., and for 100 ctm. is 0·1 grm.

The daily and hourly variations existing in the same individual under conditions of health are very great. Thus, Neubauer found that the daily maximum in one individual was 2·16 grm., the minimum, 1·21 grm.; in another, the maximum was 4·88 grm., the minimum, 2·44 grm.; Mosler found as the maximum, 4·86 grm., as the minimum, 2·40 grm., etc. Still greater differences are found when the hourly amounts eliminated are compared with each other. I found in a long series of observations in the same individual that the maximum hourly elimi-

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xi., p. 478. H. v. Haxthausen, *Acidum phosphoricum urinæ et excrementorum*, Diss. inaug., Halle, 1860. E. Bischoff, *Die Ausscheidung der Phosphorsäure im Thierkörper*. A. Riesell, *Ueber die Phosphorsäureausscheidung im Harn bei Einnahme von kohlensaurem Kalk* (Hoppe-Seyler, *Med.-chem. Untersuchungen*, Heft 3, 1868).



nation was 0.216 grm., the minimum, 0.085 grm.; both extremes occurred on one day, while the whole series of observations lasted during ten days.

The observations of Winter, Mosler, Haxthausen, and myself, which exactly agree, show that the hourly elimination of phosphoric acid is very regular, and in all of the individuals examined by us shows a very uniform course. It begins to rise in the afternoon hours (after the principal meal), reaches its maximum in the evening, falls during the night, and reaches its minimum in the forenoon hours.

The following table shows these differences in the various portions of the day in four individuals. The amount of  $\text{PO}_5$  eliminated in one hour :

		Afternoon.	Night.	Forenoon.
By A,	was	0.18	0.20	0.13 grm.
" B,	"	0.28	0.21	0.11 "
" C,	"	0.18	0.16	0.10 "
" D,	"	0.11	0.14	0.11 "

This table is instructive by showing how every general rule is modified in different persons by the individual peculiarity. In B, the curve is the steepest, the difference between the afternoon and the forenoon being the greatest. In this case, the greater part of the  $\text{PO}_5$  taken with the food was eliminated quickly, the summit of the curve falling in the afternoon hours. In the case of C, the elimination took place more slowly, the summit of the curve falling in the evening hours. In the case of D, the elimination occurred still later, perhaps on account of slower digestion, and the summit of the curve fell in the night hours, although D took his principal meal at the same hour as A, B, and C, at one o'clock P.M.

As to the *causes* upon which the increase or the diminution of the phosphoric acid elimination with the urine depend, the facts thus far obtained teach us the following:

1. The phosphoric acid in the urine increases after taking phosphoric acid or soluble phosphates into the organism.

Aubert\* found that the amount of  $\text{PO}_5$  evacuated with the urine, the normal amount in twenty-four hours being 2.8 grm.,

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\* Henle u. Pfeuffer's Zeitschrift für ration. Medicin., 1852, ii. 3.

rose after the ingestion of 31 grm. of sodic phosphate to 4.1 grm.

Von Haxthausen found also that there was a regular increase in the elimination of phosphoric acid with the urine after taking sodic phosphate.

2. The phosphoric acid in the urine increases or diminishes according as more or less phosphoric acid already formed, or substances which are capable of being transformed in the body into phosphoric acid are taken into the organism with the food. It diminishes during fasting, but without entirely disappearing during long-continued starvation, as is the case with the chlorine. As a rule, a greater amount is eliminated upon a meat diet, a less upon a vegetable diet.

Mosler found that during fasting the  $\text{PO}_4$  diminished almost one-half; and that it increased almost to double its original amount upon a diet rich in protein substances.

Schmidt observed that a cat weighing 1 kilogr. upon an unrestricted diet eliminated in twenty-four hours 0.30 grm.  $\text{PO}_4$ , but on long fasting only 0.107 grm.

The fact which was proved with certainty above in the case of chlorine, and was shown to be very probable in that of sulphuric acid, that their elimination depends not merely upon the amounts taken into the organism from without, but that it is also regulated by conditions lying within the system, changes of metamorphosis, etc., applies also without doubt to that of phosphoric acid. Many facts speak decidedly in favor of this view. It has been already shown above, that different individuals eliminate the phosphoric acid taken with the food with varying rapidity. It follows, from the observations made by me, that a remarkable diminution of the phosphoric acid elimination (0.084 grm. per hour) may succeed a temporary increase of the same (0.216 grm. per hour). The phosphoric acid elimination is, as a rule, increased by drinking abundantly of water simultaneously with that of the urea and chlorine, and, indeed, by an amount much greater than that of the phosphates contained in the water; it is, therefore, caused either by the increase of the general metamorphosis, or by the increase of the excretory activity of the kidneys, or by both together. It follows certainly, from these facts, that the organism under certain conditions may contain an increased amount of phosphates

on account of the retention of those ingested, or a diminished amount on account of their increased elimination. It is also certain that the knowledge of these conditions has the greatest importance for the physiologist as well as the physician, but what we do know at present concerning them is partly fragmentary and partly conjectural, possessing no certainty, but at the most probability. Although it now appears important and even necessary to explain these conditions by accurate series of investigations, yet we meet the same obstacles which were brought forward above in reference to the determination of the analogous conditions in the case of chlorine and sulphuric acid. One of these is that all of the phosphoric acid is not eliminated by the kidneys, but the *fæces* also usually contain phosphates.\* Therefore, either the amount of the phosphoric acid contained in different parts of the body under different circumstances must be quantitatively determined by a very large series of investigations, or the amount ingested with the food, etc., together with that eliminated with the urine and *fæces*, must be accurately estimated. But this wish must remain for a long time ungratified on account of the difficulty of the circumstances, and until then our ideas concerning the increase or diminution of the phosphoric acid in disease must be only conjectural, and it is not my intention to enter more fully into this subject here.

Riesell found that the amount of phosphoric acid eliminated with the urine was diminished after the ingestion of a large amount of chalk, since a large portion of it combined with calcium passed with the *fæces*. This diminution, however, was only temporary (two days), since the phosphate of calcium formed in the intestine was later absorbed and eliminated with the urine.

Direct investigations, of which I possess a large number

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\* Upon this point Von Haxthausen has performed some experiments under my direction. He found that the following amounts of phosphoric acid—obtained, not by ignition, but by extracting the *fæces* with dilute nitric acid—were evacuated with the excrement in twenty-four hours: Average (of seventeen observations) = 0.666 grm.; maximum = 1.080 grm.; minimum = 0.270 grm. Hence, the amount separated with the urine is four or five times greater than with the *fæces*. Riesell (see above) found that the amount of phosphoric acid in the *fæces* was increased by the ingestion of chalk.

(more than 1,000), as to the amount of phosphoric acid eliminated by patients, have taught me the following:

In acute diseases of a mild grade the following course of the elimination is frequently observed: It diminishes somewhat during the first days, probably on account of the scanty diet, then increases again gradually as the patient eats more. It sometimes exceeds the normal during convalescence with the increased ingestion of food.

In diseases of this kind of short duration, even when they are accompanied by severe fever, the diminution of the phosphoric acid is sometimes very inconsiderable and scarcely observable.

*Examples.* In a young man with severe angina tonsillaris febrilis the  $\text{PO}_4$  on the day of his entrance into the hospital amounted to 2.8 gm. An emetic was given, followed by violent vomiting. Scanty diet. On the next day  $\text{PO}_4 = 1.7$  gm. Patient became better,  $\frac{1}{4}$  diet. On the following day  $\text{PO}_4 = 2.6$  gm.; on the next 2.5 gm.,  $\frac{1}{2}$  diet. On the following day 3.2 gm.  $\text{PO}_4$ . Discharged well.

Pneumonia levior. The patient was able to be discharged well after eight days.  $\text{PO}_4 = 2.4—2.5—2.9—2.4—2.3$  gm.

Severe pneumonia, at the height of the disease: 1.7—0.8—2.1—1.2—0.9—2.1—1.9—1.1 gm.

Severe pneumonia: 1.6—1.4—2.2—2.3—1.6 gm.

Bronchial catarrh with fever: 1.4—1.5—1.7—1.5—2.8 gm.

Convalescence from a severe pneumonia: 3.8—2.7—3.2—3.5—3.9—1.8—2.5 gm., etc.

The same: 1.9—5.6—2.8—1.5—3.2—2.8 gm.

Convalescence from a severe febrile bronchial catarrh: 4.8 gm.

Catarrh. organ. digest. eczemat. with violent fever. Rapid progress, so that the patient was able to be discharged well in eight days: 2.3—2.6—2.7—2.6—3.4 gm.

#### *Females.*

Rheumatic fever: 2.1—2.3—2.2 gm.

Gastric catarrh: 1.1—1.2 gm.

Catarrhal fever: Height of the disease = 1.6 gm.

Convalescence from typhoid fever = 5.2 gm.

In many cases in which the disease is severe and the food is

withdrawn for a long time, or toward death, the phosphoric acid is much diminished.

*Cases.* Girl with severe catarrh. pulmon. febrilis. At the height of the disease = 0.7—0.5 gm. During convalescence = 1.3—2.5 gm.

Toward death in a case of acute pulmonary tuberculosis: 0.4—0.4—0.3—0.3—0.2—0.1—0.08 gm. (day of death).

Pulmonary gangrene with fatal termination: 3.0—2.5—2.2—0.7 gm.

In individual cases, however, the PO<sub>4</sub> may, during the height of an acute disease, considerably exceed the normal, as the following case shows:

Severe pneumonia in a man of middle age, who was treated and cured with large doses of digitalis: 4.3—5.1—4.1—8.4—7.9 4.5—2.9—5.0 gm.

In chronic diseases the elimination of phosphoric acid shows a very irregular progress; it usually remains below the normal, but sometimes increases considerably. Since I possess a large number of series (30–40 observations) of investigations in cases of this kind, the complete report of which would be tedious, I will in the following cases give only the mean, maximum, and minimum values.

#### *Males.*

*Cases.* Pulmonary emphysema. Mean of eight days = 1.3; max. = 2.3, min. = 0.6 gm.

Chronic bronchorrhœa. Mean of eight days = 2.7; max. = 4.7, min. = 1.3.

Carcinoma of the liver. Mean of eleven days = 2.2; max. = 2.6, min. = 1.6 gm.

Subacute articular rheumatism. Mean of eighteen days = 2.4; max. = 3.1, min. = 1.7 gm.

Hemiplegia following apoplexy. Mean of thirty-five days = 2.7; max. = 5.2, min. = 1.0 gm.

Hydruria. Mean of three days = 5.0; max. = 5.8, min. = 4.4 gm.

Dropsy. Stage of diuresis with great increase of the chlorine eliminated. Mean of two days = 1.8 gm.

#### *Females.*

Diabetes insipidus. Mean of fourteen days = 4.8; max. = 7.8, min. = 3.2 gm.

Ascites. Mean of fifteen days = 3·0; max. = 4·7, min. = 1·7 gm.

Chronic rheumatism. Mean of seven days = 3·3; max. = 4·2, min. = 2·7 gm.

Spinal irritation. 2·1—2·8 gm. Mean = 2·4 gm.

Amenorrhoea. 2·1—2·3 gm. Mean = 2·2 gm.

Scrofula. 2·6—5·2 gm. Mean = 3·5 gm.

Pulmonary tuberculosis. 1·5—3·9 gm. (ten days).

Chronic facial erysipelas. 1·5—3·6 gm. (eleven days), etc.

Brattler gives the following resumé of his investigations in disease: The elimination of phosphoric acid is diminished in diseases and functional disturbances of the kidneys with generally diminished secretion of urine (*Morbus Brightii*, heart lesions), and in diseases of the digestive organs which diminish the absorption of the food ingested. It is increased in acute febrile diseases by the increased decomposition of the tissues containing phosphorus (the increase, however, is never as constant as in the case of urea), and further in those diseases in which by a functional disturbance of the kidneys the phosphoric acid has been held back and accumulated in the blood, after removal of the obstruction (*Morbus Brightii*, and cholera).

Haxthausen observed a diminution of the phosphoric acid<sup>\*</sup> elimination in intermittent fever during the interval.

E. Mendel<sup>\*</sup> found that in chronic diseases of the brain the amount of phosphoric acid eliminated is, both absolutely and relatively to the amount of the other solid constituents in the urine, less than in healthy persons who eat the same food; that in maniacs its amount is still less, and increases with recovery; that, on the contrary, it is increased after apoplectic and epileptic attacks. In some cases, after sleep was produced by chloral hydrate or bromide of potassium, he found the phosphoric acid surprisingly increased.

### Earthy Phosphates.

#### § 132. CALCIUM. MAGNESIUM.†

In order to estimate quantitatively the amount of earthy (cal-

<sup>\*</sup> Die Phosphorsäure im Urin von Gehirnkranken, Archiv f. Psychiatrie, 1872, iii., p. 686, *et seq.*

† Beneke, Der phosphorsaure Kalk, etc., Göttingen, 1850. Derselbe, Zur

cium and magnesium) phosphates in the urine, different methods may be used according to the purpose of such investigation.

1. The amount of earthy phosphates is determined collectively according to Beneke's method. (§ 91, 1.) This method gives a result very quickly, but naturally is only suitable for approximate estimations.

2. The amount of the earthy phosphates is estimated collectively according to page 255, b, by precipitating them with ammonia, washing the precipitate, dissolving in hydrochloric acid, and estimating the phosphoric acid in the solution volumetrically. In this way the true weight of the earthy phosphates is not found, but only that of the phosphoric acid combined with the earths.

Or we may estimate :

3. The calcium and magnesium according to § 76.

In order to be able to draw further conclusions from the results which have been obtained by the one process or the other, the following may serve as indications :

Beneke considers 1·2 gram. as the normal quantity of earthy phosphates which are passed with the urine in twenty-four hours by a healthy active man.

Lehmann passed in twenty-four hours

With ordinary diet, . . 1·09 gram. of earthy phosphates.

With purely animal diet, 3·56 " " "

Böcker evacuated on the average 1·48 gram. daily.

Mosler found that the amount of phosphoric acid combined with the alkaline earths (not earthy phosphates, therefore), was in his own case, I., during six days in April; II., during four days in October :

	I.		II.	
	Per Day.	Per Hour.	Per Day.	Per Hour.
Mean, .	1·152	0·048	0·390	0·015 gram.
Maximum,	1·800	0·075	0·660	0·027 "
Minimum,	0·370	0·015	0·170	0·007 "

Physiologie und Pathologie des phosphorsauren und oxalsauren Kalkes, 2. Beitrag, Göttingen, 1850. Kletzinsky, Heller's Archiv, 1852, p. 270, *et seq.* C. Neubauer, Ueber die Erdphosphate des Harns, Journ. f. prakt. Chem., Bd. 67, p. 65, *et seq.* F. Huenke, De phosphatum terrarum in urinæ quantitate, Diss. inaug., Berlin, 1859. A. Riesell (see the preceding section). S. Soborow, Ueber die Kalkausscheidung im Harn, Centralbl. f. d. med. Wiss., 1872, p. 609.



In another healthy individual the hourly mean was from 0·015 to 0·019 grm.

Hegar found that the mean amount of phosphoric acid combined with the alkaline earths was, in his own case, 1·31 grm., the observation lasting eight days; a half year later the mean daily amount of a four days' observation was 0·902 grm.

Neubauer obtained, as the result of very numerous investigations, the following values, which deserve the greatest confidence on account of the great number of observations (52) and the accuracy of the methods employed.

The average mean amount of earthy phosphates which are passed with the urine by an adult man in twenty-four hours, is from 0·941 to 1·012 grm. The average maximum=1·138 to 1·263 (highest number=1·554). Average minimum=0·8 (smallest amount=0·328 grm.).

The daily amount of calcic phosphate averaged 0·31—0·37 grm. Its average maximum=0·39 to 0·52 grm. (largest amount=0·616 grm.). Average minimum=0·25 (smallest amount=0·15 grm.).

C. Bödeker\* found that the daily amount of CaO passed with the urine by nine young men varied from 0·2 to 0·6 grm. The mean was 0·32 grm.

The magnesian phosphate averaged 0·64 grm. The average maximum=0·77 (largest amount=0·938 grm.). Average minimum=0·5 grm. (smallest amount=0·178 grm.).

On the average, therefore, one equivalent of the phosphate of calcium is evacuated to three equivalents of the phosphate of magnesium, or in 100 parts 33 of calcic phosphate and 67 of magnesian.

According to the investigations of Neubauer, calcium salts when ingested do not appear in the urine, or only to very slight extent. On the contrary, W. Roberts found that after eating, the earthy phosphates were considerably increased in the urine, almost doubled.

The experiments of A. Riesell show that an increase of earthy phosphates in the urine took place after the ingestion of a large amount of chalk, and at the same time an increase in proportion to the amount of phosphoric acid combined with the alkalies. He found that under normal conditions of the

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\* *Zeitschr. f. ration. Med.*, 1861, p. 164, *et seq.*

total amount of phosphoric acid contained in the urine (from 2·7 to 2·9 gm. in the twenty-four hours) about  $\frac{2}{3}$  was combined with the alkalies and  $\frac{1}{3}$  with the alkaline earths. After the ingestion of chalk, however, the proportion changes during the first two days to about equal parts ( $\frac{1}{2} : \frac{1}{2}$ ), together with a diminution in the total amount of phosphoric acid contained in the urine (from 1·3 to 1·6 gm. in twenty-four hours), while there is an excess in the fæces. In the next two days, when the amount of  $\text{PO}_4$  has again increased in the urine (2·2 gm. in twenty-four hours), the proportion becomes reversed, so that about  $\frac{2}{3}$  of the phosphoric acid eliminated with the urine is combined with the alkaline earths and only  $\frac{1}{3}$  with the alkalies. During these last two days the urine also contains a sediment of the phosphate of calcium, which had formed within the urinary passages.

In *disease* the absolute amount of the earthy phosphates as well as the relative proportion between the calcic and magnesian phosphates appears to vary very much from the above-mentioned normal. Thus it is almost universally accepted that in certain diseases of the bones (osteomalacia, rachitis, etc.) the elimination of the earthy phosphates, especially of calcic phosphate, with the urine is very much increased. For the complete explanation of this symptom, important not merely to the pathologist but also to the therapist, still more numerous and careful investigations are desirable. But these, in order to give information concerning the metamorphosis of the earthy phosphates as they naturally would, must take account of the earthy phosphates eliminated not merely with the urine but also with the fæces.

An increase of the earthy phosphates, especially of the calcic phosphate, has special importance to the physician, when it leads to the formation within the urinary passages of a sediment which may give rise to the formation of urinary gravel or calculi. For further particulars on this point consult § 135, under the head of calcic phosphate calculi.

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The urinary constituents considered in the previous sections are those whose quantitative estimations are, for the purposes of the practising physician, of especial importance, since they give the most indications for judging of the processes of meta-

morphosis in the body, and, moreover, the methods of their quantitative analysis are relatively simple.

In certain cases, however, it is desirable to estimate the amount of some other urinary constituents, normal and abnormal. We will consider these in the following section.

§ 133. POTASSIUM. KREATININ. LEUCIN AND TYROSIN. ALLANTOIN.  
LACTIC ACID. OXYMANDEL ACID. CARBONIC ACID.

The quantitative estimation of the amount of potassium eliminated with the urine is performed according to the familiar methods. (Compare § 78 and § 79.) In many cases this is of interest to the physician, since a diminution as well as an increase of this substance in the organism is regarded by many as the cause of diseased disturbances. The statements of Weidner may assist in judging of the results obtained by such investigations. This observer evacuated in twenty-four hours on the average 3.91 gm. of KO (max. = 59, min. = 2 gm.). He found that the proportion of potassium and sodium in the urine was as 1 : 1.35.

*Kreatinin.* For its properties consult § 3, and for the methods for estimating it in the urine § 74.

The average daily amount in the urine of men is about 1 gm.

Neubauer\* found in his own urine from 0.6 to 1.3 gm., mean = 1 gm. of kreatinin. In several other adults he obtained the same results (0.8—0.9 gm. per day). Loebe† obtained a similar average (0.839 gm. per day) from ten observations upon two men. K. B. Hofmann‡ found in twenty-seven observations upon himself as the daily average 0.681 gm. (max. = 0.810, min. = 0.519 gm.). In other persons he found somewhat more : mean = 0.99 gm. per day. The urine of infants (nursing) contains no kreatinin. Women eliminate somewhat less than men. The daily average in women (of seven observations) was 0.65 gm.

The kreatinin of the urine originates from the kreatin of the muscles, which, before it has left the body (probably in the

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\* Annal. d. Chem. u. Pharmac., Bd. 119, page 27, *et seq.*

† Journ. f. prakt. Chemie, 1860, page 170, *et seq.*

‡ Virchow's Archiv, 1869, Bd. 48, page 358, *et seq.*

kidneys), is changed into kreatinin. The muscular tissue of the meat which is eaten partly contributes to this, and partly the muscles of the body, when they are decomposed by metamorphosis. An increased muscular activity, when not accompanied by a chemical decomposition of the muscular tissue, produces no increased elimination of kreatinin, as Nawrocke,\* Voit,† and Meissner‡ have shown.

Hofmann found that the amount of kreatinin in the urine diminished during starvation. It was considerably increased by a meat diet even in children, who otherwise eliminated little or no kreatinin with the urine. Bodily activity, on the contrary, had no influence upon the amount of kreatinin.

We must consider also the increase or diminution in the elimination of kreatinin with the urine in *pathological* cases. In this respect the facts hitherto obtained teach us the following: Munk found the kreatinin increased in the urine in acute diseases, like pneumonia, the efflorescent stage of typhoid, and intermittent fever, and diminished during convalescence from acute diseases. Hofmann came to the following conclusions: Purely local affections were without influence; febrile diseases produced an increase (at the expense of the muscular tissue of the body); diseases attended with scanty nourishment produced a diminution. In advanced degeneration of the kidneys the amount of kreatinin in the urine diminished even when an abundance of meat was eaten (probably because the kidneys were unable to change the kreatin present in the blood into kreatinin). H. Senator § found it considerably diminished in the urine in two cases of tetanus—a disease in which, however, there is an excessive activity of the muscles. This fact, which is according to the earlier opinions an apparent paradox, finds its explanation in the above-mentioned experience of Voit and others.

Whether there is an increased elimination of kreatinin or not in trichinosis, as would be expected, must be decided by further investigations.

*Leucin* (see § 36) and *tyrosin* (see § 37, § 48, and page 425)

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\* Centralbl. f. d. med. Wissensch., 1866, page 625.

† Zeitsch. f. Biologie, Bd. 4, page 114, *et seq.*

‡ Zeitsch. f. ration. Medic., 1868, Bd. 31, p. 234, *et seq.*

§ Ueber die Beschaffenheit des Harnes im Tetanus. Virchow's Archiv, Bd. 48.

usually occur together. They are the products of the decomposition of nitrogenous substances, and are, therefore, found in parts of the body which have been preserved for a long time in alcohol, whereby the tyrosin which is insoluble in alcohol separates in the form of a white deposit. When the metamorphosis is normal, they form in the body in, at the most, small amounts; but when there is an abnormal, putrefaction-like decomposition (gangrene, etc.), they form in larger quantity. In such cases they may also pass over into the urine, and their importance for the physician rests upon this, that from their abundant presence in the urine we may infer the existence of such an abnormal decomposition within the organism. They take the place of the diminished, or even absent, urea (compare page 478). Up to the present time they have been found especially in acute atrophy of the liver and in acute phosphorus poisoning, and in a few cases of leucocythæmia, typhoid, small-pox, etc.\*

The presence of *allantoin* in the urine has, up to the present time, but slight importance for the physician. It has been found by Frerichs and Städeler in the urine of dogs when the respiration has been impeded; also by Köhler.† Schottin‡ found it in the urine of men also after taking tannic acid.

The presence of *lactic acid* (§ 30) and *oxymandel acid* (§ 38) in the urine of persons suffering with acute atrophy of the liver, need only be mentioned here.

A. Ewald § has in a number of cases of persons suffering with acute diseases determined the amount of carbonic acid in the urine, and has found that it is regularly higher during the febrile stage than when there is no fever.

The quantitative estimations of *albumen* and *sugar*, which are sometimes necessary, have been already treated in § 97 and § 104.

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\* Compare Frerichs and Städeler in Müller's Archiv f. Anat. und Physiol., 1854, page 893, *et seq.* Schmeissner, Archiv d. Pharmac., October, 1849, Bd. 150, page 11. O. Schultzen und L. Riess, Ueber akute Phosphorvergiftung u. Leberatrophie, Berlin, 1869.

† De allantoini in urina impedita respiratione præsentia, Diss. Halens, 1857.

‡ Lehmann's Hdbch. d. physiol. Chemie, 1859, page 93.

§ Ueber den Kohlensäuregehalt des Harns, Archiv von Reichert und DuBois-Raymond, 1873.

## § 134. CONCLUDING OBSERVATIONS.

The attempt has been made above to explain the importance of the quantitative changes of the urine for the physician, in such a way as to include the semiology and significance of the different diseases. But the information, which the physician may obtain from the observation of the urine in disease, has by no means been exhausted. He is enabled to draw still more important conclusions in reference to diagnosis, prognosis, and treatment than the *single* changes in the urine warrant in themselves by observing various changes which are present simultaneously or follow each other closely, or even by going a step farther and comparing these with abnormalities in other secretions, as the intestinal, the lung exhalations, the perspiration, etc., which give him information as to the general metamorphosis in the organism. It is not my intention to go any farther into this domain, which is still enveloped in darkness, and has, for the most part, only recently been investigated. I wish only to give a few cases from which the physician can draw important inferences, and with relatively little trouble. The following cases have all been taken from real life, and have been observed by me in the manner to be described. In order to avoid being tedious, I only give a sketch of them, bringing out the principal features, and adding a few general observations, where necessary for an explanation:

1. A girl, 20 years old, who had been ailing for a long time and suffering with indefinite symptoms, which were considered to be due to beginning pulmonary tuberculosis, had great thirst, diminished perspiration, and no fever. She passed a very large amount of urine (3,000 to 6,600 cc. daily) of high specific gravity (1.025 to 1.034), and it contained a considerable amount of *sugar*. The diagnosis was without any doubt diabetes mellitus. After the use of an animal diet, meat and gluten bread, together with the administration of alkalies (magnesia and bicarbonate of sodium) and opium, improvement took place, but it was not of long duration. An intervening pneumonia fulminans quickly proved fatal.

In contrast to this case of decided diabetes mellitus, the author has during the last year observed a large number of cases in which the urine has contained sugar, usually tempo-

rarily and after the ingestion of smaller or larger amounts of sugar, without the general health being disturbed thereby to any great extent. This occurred usually in men of advanced life (although there were a few cases in women) who lived well and suffered more or less with symptoms of arthritis (rich man's gout, podagra, etc.). In some of these cases the urine contained, together with the sugar, considerable quantities of albumen also. Some of these patients the author has had under his observation and treated (usually with slight attacks) for a long time (ten years and more), without having seen any dangerous complications occur, or even with only a slight disturbance of the general health.

Possibly this report may serve to give consolation to those patients to whom the fear brings more danger than the disease itself: that glycosuria is not in all cases dangerous.

2. A woman, 36 years old, with a puffy, pale, anæmic look, and blue rings about the eyes, suffered with all sorts of nervous symptoms (mental hyperæsthesia with a tendency to spasms), such as are ordinarily included under the name of "hysteria." A more accurate examination showed that the amount of urine passed was very much increased (between 3,000 and 4,000 cc.). The urine was pale yellow to bright yellow, its coloring matters were rather diminished than increased (3 to 5); it was only feebly acid, even frequently alkaline, and the free acid was decidedly diminished (0 to 0.5). Its specific gravity was below the normal (1.012 to 1.015), but the amount of the solid constituents was decidedly increased (80 to 120). This increase included most of the urinary constituents (urea 40 to 49, chlorine 20 to 30, phosphoric acid 5 to 9, and sulphuric acid 3 to 5 gm.). The urine contained no trace of sugar. Diagnosis: diabetes insipidus. The patient obviously suffered from an abnormal increase of the metamorphosis of tissue (only that of the blood globule being decidedly diminished, and the temperature was also below the normal), the emunctories of the body were almost all increased, and since the patient lived in poor circumstances, this increased elimination could not be made up by an abundant ingestion of food, so that her nutrition rapidly fell: she lost in weight about three pounds in two days. With an abundant amount of concentrated food combined with tonics (preparations of quinine and iron) and opium, the secretion of



urine gradually became normal, the appearance of the patient improved, her strength increased, and the nervous symptoms disappeared. Since, however, the patient returned to her former way of living, the attacks were repeated—diabetes insipidus intermittens.

I have frequently observed exactly analogous cases in consequence of drinking an excessive amount of water after the careless employment of water cures, undertaken in consequence of false indications or continued for too long a time.

3. A strong man, in consequence of exposure to cold, was seized with severe tearing pains in the region of the neck and shoulder (*rheumatismus nuchæ*). The skin became cool and dry, and the amount of perspiration diminished; his urine, however, was increased (3,000 to 4,000 cc.). The amount of coloring matter in it was about normal (4 to 5), and also that of the free acid (1·8 to 2·3). Its specific gravity, however, was far below the normal (1·006 to 1·008), and the amount of the total solid constituents was rather diminished (36 to 40 grm.), also that of the individual substances, the urea, chlorine, phosphoric acid, and sulphuric acid was rather below than above the normal. Diagnosis: hydruria. The increase of the urine was evidently only dependent upon an increased elimination of water by the kidneys, which made up for the diminished separation of water by the skin and lungs. Although the hydruria continued for several days, yet the strength and weight of the patient did not diminish. After treatment with diaphoretics, which produced an increase of the perspiration, the polyuria gradually disappeared, and also, after the use of wet cups, the *rheumatismus nuchæ*.

4. In the case of a young man with organic heart disease (insufficiency of the bicuspid valve with consequent hypertrophy and dilatation of the right ventricle), the amount of urine gradually diminished (from 1,600 to 1,200, 800, and 600 cc.); at the same time the elimination of the urea (26, 20, 18 grm.) and chlorine (8, 5, 3, grm.) diminished considerably, and to a less extent that of the phosphoric acid (2 to 1·5 grm.) and sulphuric acid (1·5 to 1 grm.). Dropsical effusion into the abdominal cavity and cedematous swelling of the extremities, especially the lower, followed. After the administration of powerful diuretics (infusion of digitalis and acetate of potassium) the amount

of urine increased considerably (3,000, 4,000, 4,500 cc.), and with this very considerable amounts of urea (50, 55, 60 gm.) and chlorine (25, 30, 33 gm.) were eliminated, while the sulphuric and phosphoric acids scarcely exceeded the normal amount. In this case evidently large quantities of water, urea, and chlorine, instead of being evacuated with the urine, had gone over into the dropsical effusions and had accumulated in them, and after the abundant diuresis were separated with the urine.

The same course, diminution of the secretion of urine, and simultaneous dropsical swellings with an increased elimination of water, urea, and chlorine with the urine after the use of diuretics, was repeated several times afterward in the same case.

5. An elderly man, who suffered with a very marked rigidity of the arteries, was attacked with a pretty severe bronchitis, extending over both lungs. The condition of the patient was subject to extraordinary variations; violent attacks of dyspnoea with a small rapid pulse of 100 to 126 beats, which sometimes caused fainting, alternated with a tolerable condition. The examination of the urine showed that there were similar variations in the metamorphosis of tissue, which ran a parallel course with the general condition of the patient. On some days only 300 or 400 cc. of urine were passed, and on others 1,200 to 1,500 cc. Its color varied from bright yellow to red; the coloring matter, from 2 to 18, was, however, as a rule, increased (influence of the fever); the specific gravity was about the average (1.012 to 1.023), the amount of solid constituents was, on the average, far below the normal (18 to 30 gm.), the amount of urea was also very varying, but was also, in spite of the fever, far below the normal (12 to 25 gm.); the urine frequently contained a sediment of urates. The chlorine showed the greatest variation; it was always considerably diminished, and sometimes only traces were found in the urine (0.1 to 5 gm.). The phosphoric and sulphuric acids were also diminished. These considerable variations in the metamorphosis of the patient, depending upon a shattered constitution, taken in connection with the existing lung disease, led to the fear of a speedy collapse. In fact this took place very suddenly. On one evening after the patient felt better and more brisk than usual, he complained of great weakness in the night, and a rapidly spreading oedema of the

lungs, which withstood all counter-irritants used, proved fatal in a few hours.

6. A man, 57 years old, in consequence of a severe exposure to cold upon a journey, was attacked with a pneumonia of the left side, which was, from the beginning, treated with cupping and digitalis in large doses ( $\frac{1}{2}$  drachm daily). The patient had very severe fever; the urine was less scanty than in other similar cases (at the height of the disease, 900, 1,000, 1,950, 1,500, 1,350, and 1,200 cc.), very high colored, the amount of coloring matter considerably increased (28 to 32), the specific gravity about normal (1.018 to 1.024), and the solid constituents usually below but sometimes above the normal. The urea was increased (40 to 60 grm.), the sulphuric acid at first increased (3.5 to 4 grm.), but later was below the normal (1.8—1.1—1.6 grm.), and the phosphoric acid was almost always increased (4—5—7—8 grm.). The chlorine, during the first two days, was present only in traces, increased gradually (3—4—7 grm.), and reached the normal from the eighth day. The patient improved very rapidly in spite of his advanced age, and in spite of the fact that he had previously had pneumonia, so that his lungs were probably not entirely normal, and was able to leave the hospital well in ten days. This case is especially interesting in reference to the metamorphosis, since it shows the favorable action of the digitalis. There was in this case, as in all violent fevers, an increased decomposition of the constituents of the body, and unusually large quantities of urea and urinary coloring matter were formed, and increased amounts of phosphoric and sulphuric acids were set free from their organic compounds. But the secretion of urine was, in this case, owing no doubt to the influence of the digitalis, much more abundant than in other similar cases, whereby the decomposition products formed were quickly separated from the body, and convalescence hastened. I do not mean to say that the action of digitalis in such cases is limited to this effect, but only mention that method of action as an apparent one in this case.

7. A man suffered with a chronic affection of the liver and stomach with organic change which could be ascertained, although its exact nature could not be diagnosticated. Long-continued disturbances of digestion and severe pain had exhausted his strength, and, therefore, it was desirable to obtain a nearer

insight into the metamorphosis of the patient, partly to establish the indication for the means to be first used for the symptoms, and partly for the purpose of giving a prognosis. For this reason the patient's urine was examined for several days in succession, and the following were obtained as the average proportions: The quantity was about normal (1,500 cc.), the color bright yellow, the coloring matter somewhat below the normal (3), the reaction feebly acid, and the free acid considerably diminished (0.4). The specific gravity was somewhat low (1.014), and also the solid constituents (42 grm.); of the single constituents, the urea (29 grm.) and sulphuric acid (1.4 grm.) were somewhat diminished, while the phosphoric acid (3.3 grm.) was about normal, and the chlorine (10 grm.) was rather in excess of the normal. This showed at that time a good condition of the digestion (chlorine and  $\text{PO}_5$  abundant), but, on the contrary, a somewhat diminished decomposition of the nitrogenous tissues (urea and  $\text{SO}_3$  below the normal), and also a diminished metamorphosis of the blood globule (small amount of pigment and considerable diminution of the free acid). The last part of the diagnosis was confirmed by the pale anæmic appearance of the patient. In consequence of this information the patient received a good diet, with tonic drugs, whereby his strength and vital energies were, for a time at least, increased, although the complete cure of the organic changes forming the principal trouble could not be expected.

8. There are cases in which a febrile increase of the metamorphosis can be recognized almost solely by the composition of the urine. The pulse is entirely quiet, the temperature of the external parts of the body scarcely increased, the appetite but little diminished, and yet there exists an increased tendency to the decomposition of the constituents of the body and a cessation of the excretory activity of the kidneys, a condition which may be especially dangerous when, with an existing disease of an important internal organ, like the lungs, liver, etc., it gives rise to congestion of this organ, which, if long continued, easily leads to organic changes or increases any such already present. The following is a case of this kind.

A very powerful man, 48 years old, with a broad, full chest, came with symptoms which pointed to a commencing pulmonary tuberculosis. He had for a long time had a cough with

expectoration, slight dulness of percussion over the apex of the right lung, with ill-defined, almost bronchial, respiration and rales at this point. His respiratory power was less than corresponded to the size of his body; fulness of body and strength had diminished somewhat during the last month. His pulse was, however, entirely quiet (60 to 63), his appetite was tolerably good ( $\frac{1}{2}$  diet with various extra dishes), the temperature of the extremities was not increased, and only in the night there was sometimes profuse perspiration. The urine, on the contrary, was remarkably abnormal; it was very much diminished (400 to 600 cc.), almost always turbid, with a sediment of uric acid; very high colored, and the coloring matter increased (16 to 24); the specific gravity was very high (1.022 to 1.028), the urea was rather above the average (28 to 35 grm.), the chlorine very much diminished (3 to 5 grm.), and the phosphoric acid (2.5 grm.) and sulphuric acid (1.6 grm.) were somewhat below the normal. The excretory activity of the kidneys was, therefore, decidedly diminished, and since at the same time the decomposition of the constituents of the body was increased, the blood was overcharged with irritating ingredients. It happened that the patient had for a long time previously suffered with a chronic skin disease (probably psoriasis), which had disappeared six months before. There existed here, therefore, several conditions together, which must have caused an excessive activity of the lungs, and thereby an increase of the disorganization to be expected in them. (An accurate examination revealed, in spite of the slow and quiet arterial pulse, an increased activity of the right ventricle of the heart and an evident strengthening of the pulmonic second sound, an overloading of the lungs with blood: at the same time the patient complained of considerable dyspnoea and tightness of the chest.) The principal indication appeared to be to free the lungs of the patient from the irritation caused by the accumulation of excrementitious substances in the blood by increasing the secretion of urine. He was given mild diuretics and blood-purifying drugs (infusion of digitalis with acetate of potassium; a tea of the *viola tricolor*). In general, as the secretion of urine increased, the patient felt freer in the chest, and much more comfortable in his general condition, so that, after a while, he was able to be discharged much improved.

Since, however, he could not and would not pursue a desirable mode of living outside of the hospital, and, moreover, was an excessive spirit drinker, the disease made new progress, and he returned to the clinic after six months with settled pulmonary tuberculosis, and died there a few days later.

9. A man, 45 years old, was attacked suddenly with all of the symptoms of a violent febrile disease : chills and heat, loss of appetite and bloody urine. Within one and a half days an oedematous swelling spread over the whole body with the exception of the face. When the patient was admitted a few days later into the clinic at Giessen, the symptoms were the same as those given except with the addition of violent vomiting. During the first three days of his stay there the urine had the following appearances : Its amount was somewhat below the normal (900 to 1,500 cc.), and its color intense blood-red. Under the microscope it was seen to contain unchanged blood corpuscles in considerable quantity, numerous pus corpuscles, and a few granular casts. It contained an abundance of albumen. The reaction was alkaline, the specific gravity was low (1.010 to 1.012), the amount of urea was far below the normal (8 to 20 gm.), the chlorine was considerably diminished (1 to 3 gm.), the phosphoric acid somewhat (1.3 to 2.8 gm.) and the sulphuric acid considerably (0.5 to 1.6 gm.) diminished. On long standing, a slimy sediment formed in the urine, due to the action of the ammonia upon the pus corpuscles suspended in it. The perspiration (sum of the evaporation from the skin and the lung exhalation) was far below the normal (460 to 780 gm. in twenty-four hours), the ingesta considerably exceeded the excreta, so that the patient increased in weight ten pounds in three days, which naturally was due only to the constantly increasing dropsical swelling. Diagnosis: *Morbus Brightii acutus*. On account of the great danger that uræmia might develop suddenly under such circumstances, the most powerful means were employed to increase the secretion of the kidneys and bowels, but without effect. All remedies taken internally (sulphate of sodium with acetate of potassium, gamboge with carbonate of sodium, croton oil) were vomited again by the patient ; applications of decoction of digitalis made over the whole body remained without effect ; enemata of croton oil dissolved in linseed oil irritated the rectum to such an extent that it was



necessary to omit them. The excretory activity of the kidneys diminished daily; the amount of urine fell from 800 to 700, 500, and 450 cc. daily, having a specific gravity of from 1·015 to 1·010. The amount of urea diminished continuously (6 to 8 grm. daily), also the chlorine (0·8 to 1 grm.), sulphuric acid (0·4 to 0·6 grm.), and phosphoric acid (1·3 to 1·7 grm.). Symptoms of uræmia (vertigo, delirium) developed, which continued to increase (coma vigil, sopor) till the patient died, scarcely three weeks from the commencement of his disease. The section showed the existence of two stages of Bright's disease in the kidneys.

10. A man, 52 years old, of strong physical constitution, was attacked with acute Bright's disease, exactly as in the above case. Considerable œdematous swelling of the whole body, followed quickly by violent febrile symptoms: the blood-red urine was rich in albumen and showed under the microscope the presence of traces of renal casts together with numerous blood and pus corpuscles. But in this case powerful diuretics (pills of gamboge and carbonate of sodium, and especially applications of the decoction of digitalis which were made on a large scale over the whole lower half of the body) succeeded in producing an abundant secretion of urine. The urine (from the 25th of October to the 1st of November) had the following properties: The amount was very much increased (4,800 to 6,800 cc.), the color was red (bloody), the reaction neutral or alkaline, the specific gravity low (1·003 to 1·005), the urea increased (between 45 and 97 grm. daily), also the chlorine (20 to 30 grm.), phosphoric acid (11 to 18 grm.), and sulphuric acid (4·1 to 4·7 grm.). With this increase in the secretion of urine the dropsical swelling disappeared entirely, the symptoms of uræmia (wandering, somnolence) which appeared at first ceased, and the patient felt very well. After a while a fresh exacerbation came on: violent fever with swelling of the lips and a phlyctænoid eruption about the mouth, more scanty and very bloody urine. Since the last symptom showed a violent inflammation of the kidneys and there was no dropsy, diuretics appeared to be no longer indicated, and I considered the principal indication to be now to act upon the kidneys with remedies to lessen the inflammation. An emulsion of cannabis-indica seeds with bitter-almond water was given,



and after two days the deep bloody urine became almost colorless.

11. *Hæmaturia, caused by dissolved hæmoglobin.* (Compare § 100.) A young man, 20 years old, always well up to the present time, complained that he had not felt well for about eight days. His face was extremely pale, livid in spots, especially under the eyes, where there were bluish-red rings; the temperature of the skin was not increased, the pulse was rapid (90 to 100), small, and feeble. There were mild, tearing, drawing pains over the greater portion of the body, especially the extremities, together with a sensation of weariness and depression. There was also a mild catarrh of the organs of respiration and digestion (loss of appetite, coated tongue, moderate diarrhoea), and slight increase in the size of the spleen. He was received into the clinic, and it was suspected that a typhoid fever was coming on. This suspicion, however, was not realized. The mild febrile symptoms diminished rather than increased, the very feeble, often dicrotic, pulse became slower and fuller, the temperature did not rise above the normal, but usually remained below 37° C., the intellect remained clear, while the patient became so weak that he could scarcely raise himself, and the anæmic livid appearance was so extreme that it reminded one of the algid stage of cholera. The urine was of normal amount, and dark brownish-red color (between 7 and 8 in the color table), similar to, although not quite as dark as, specimens which I have seen after the inhalation of arseniuretted hydrogen. (See page 392.) It contained at least 300 parts of pigment. No blood corpuscles, and in general, no morphological elements could be detected under the microscope. Upon boiling, a very abundant reddish-brown coagulum of hæmoglobin was formed, the filtrate from which had a feeble yellow color. Otherwise it contained the ordinary constituents in normal amount, only the chlorides being somewhat diminished on account of the scanty diet. This condition of the urine, which had certainly existed before the admission of the patient (he could give no explanation of it), lasted about eight days and then disappeared gradually. It indicated that the disease consisted essentially of a continued extensive decomposition of the blood globules within the blood vessels, the products of which were eliminated with the urine (perhaps

partly, also, with the bile), and which by its intensity and long duration produced an oligocythæmia of high grade. The condition of the urine together with the great depression and the pains in the limbs pointed also to scorbutus, but the change in the gums as well as the ecchymoses into the skin and subcutaneous cellular tissue, etc., were absent, and also any etiological fact which could play any part in the production of scorbutus.

The patient took mineral acids, at first alone, but later with quinine, and during convalescence preparations of iron. He recovered slowly but completely.

No cause could be discovered.

A few months later, without any cause which could be detected, another attack of hæmaturia appeared, only shorter and less intense than the former one. During this attack, as during the first one, the patient was entirely free from pain in any part of the uropoëtic system.

12. The following case, essentially different from the preceding one, and also occurring without any discoverable cause, affords an example of *vesical hæmaturia*. Friedrich P., butcher, 22 years old, never sick before, born of healthy parents (the father is said to have suffered from hæmorrhoids only), was attacked with a mild gastritis with dizziness and ringing in the ears, and was on that account admitted into the clinic. Formerly he had never had attacks of hemorrhage, but a few years before his sickness he had frequently had nose-bleed. A more accurate examination of the patient showed that his urine was blood red, and a further investigation showed that he suffered with dysuria, a frequent involuntary impulse and desire to urinate, so that he was forced to micturate almost every quarter of an hour. The urine, especially that last evacuated, was always very bloody. Examination of the orifice of the urethra showed nothing abnormal, the posterior part of the urethra was not tender on pressure, nor did the digital examination, per anum, of the prostate and bladder show any abnormality. The plainly bloody-colored urine deposited after long standing a scanty dark-red sediment, which became diffused upon shaking and which consisted only of blood corpuscles without admixture with pus. If the urine was filtered, the filtrate appeared to be completely free from blood,

of a clear yellow color, while a dark-red precipitate of blood corpuscles remained behind on the filter; the urine contained, therefore, only undecomposed blood globules and no dissolved blood pigment. The blood corpuscles came without doubt from the bladder, and the cause of their passage into the urine was probably a congestive hyperæmia of the mucous membrane of the bladder, which had increased to such an extent as to rupture the vessels.

The treatment was limited to the administration of hemp-seed tea with bitter-almond water, under which the patient improved so much that the dysuria disappeared in a few days, and the blood gradually ceased to appear.

13. The following case is interesting since it resembled most delusively a case of hæmaturia, the non-existence of which was only recognized by the microscope.

An old man, 72 years old, had had for about five years an affection of the bladder, which was chiefly characterized by the fact that the patient, who had previously been well and was for his age very robust, from time to time after straining, too long retention, etc., passed a little blood with his urine, and had slight pain in the region of the bladder. The simultaneous occasional evacuation of gravel had given rise to the suspicion that a vesical calculus might exist. He had, therefore, consulted various physicians and had been examined several times, but no calculus had been detected. Most of the physicians explained his affection by the existence of bladder hæmorrhoids, and the patient had in consequence used Kissingen and Carlsbad waters without any marked benefit. He had never lost blood with his stools. Examination showed no trace of hæmorrhoids and no enlargement of the prostate. His general health was good and his arteries were not rigid.

The urine of the patient was very strongly acid and deposited a sediment of large crystalline masses of uric acid. There was, besides, a very abundant dirty-red (cinnamon colored) sediment, in which there were large flocculi and which settled pretty quickly. Disseminated through the urine it gave it the appearance of being mixed with blood, and it had been so considered by the patient and his various physicians up to this time. Under the microscope numerous cellular forms were seen, which at first sight appeared to be blood globules, but which upon

more careful examination were seen to differ from them in important particulars. They were round and reddish colored like blood globules, but were somewhat larger ( $\frac{1}{30}$  to  $\frac{1}{20}$ " in diameter), contained a distinct nucleus, and were not changed by acetic acid. (See Plate III., fig. 6, D, a, a.) Together with these there were other larger and smaller, irregular, partly caudate cells, mostly with an overlying nucleus (Fig. 6, D, bbb), partly single, partly (in the flocculi visible to the unaided eye) united in shreds, but without any trace of a fibrinous basement membrane. The sediment also contained normal pus corpuscles, which on being treated with acetic acid showed the ordinary nuclei.

From this result the preliminary diagnosis was made of fungous excrescence (epithelioma) of the bladder, with a tendency to acid urine and the separation of uric acid, and he was ordered the regular use of Fachinger water and hemp-seed tea, with acetate of potassium and cherry-laurel water. Under this treatment the condition of the patient improved greatly. For several months in succession the urine was no longer bloody colored, and contained instead of the cells of the epithelioma only a few pus corpuscles and a few mucous shreds. The troubles of the patient were reduced to occasional pains in the glans penis, and only the evacuation of the last portion of the urine required any straining.

May the above examples contribute to convince our professional brethren that a consideration of the condition of the metamorphosis in patients is of value to the practising physician, and that an examination into this condition does not involve such insurmountable difficulties as many appear to think. But, finally, I cannot forbear to express the wish, that those physicians who undertake to follow the methods suggested above, may keep within bounds, and not by keen hypotheses and unfounded suspicions overreach the limits of our present knowledge. Such a procedure would serve not only to injure the patient who intrusts himself to his care, but also would tend to lower in the eyes of the intelligent profession, as well as of the public, the value of this certainly legitimate tendency of scientific medicine, which sets for itself the task of considering the chemistry of the metamorphosis in disease in addition to the observation of other conditions.

## APPENDIX.

## § 135. INTRODUCTION TO THE EXAMINATION OF URINARY CALCULI AND OTHER URINARY CONCRETIONS.

*Urinary concretions* are deposits which form from the urine within the urinary passages (kidneys, ureters, bladder, or urethra). They are sometimes small, like grains of sand, so that they can be passed with the urine without great difficulty, in which case they are usually numerous and, as a rule, crystalline (urinary sand, gravel). Sometimes they are larger, from the size of a bean to that of an apple, so large that they cannot, or only under exceptional circumstances, be passed with the urine, but are retained in the calices or pelvis of the kidney or in the bladder, and there produce, by their mechanical action, irritation, pain, hemorrhage, inflammation, etc., and they may also remain sticking in the ureter and urethra, and occlude, irritate, and wound these canals (*true calculi*).

Most of these concretions consist of the urinary sediments which have separated within the urinary passages, and, instead of being immediately evacuated, unite together into large masses or adhere to and incrust a foreign body which has in some way gotten into the urinary passages. In this way concretions already existing may increase in size, new layers of sediment being constantly deposited upon them, and they grow more or less rapidly.

Since transitional forms very frequently occur between urinary gravel and the ordinary sediments from which the gravel is formed, and no sharply defined limit can be drawn between gravel and the smaller calculi, the distinction between these different forms in many cases is a tolerably arbitrary one and of no great practical importance.

On account of the unpleasant and oftentimes even dangerous consequences of an existing urinary concretion, its detection is naturally of great importance to the physician. To describe the manner in which this must be done belongs to special pathology and diagnosis. But the recognition of the chemical composition of a concretion has also not merely a scientific but also a practical interest for the physician, since this only can give us the means of preventing, by appropriate medical treat-

ment, the further formation of gravel which irritates mechanically the urinary passages, or the still more dangerous formation of a calculus, or finally the further growth of a calculus already formed, if we leave out of consideration entirely those hitherto rather unsuccessful experiments of dissolving the concretions by chemical reagents within the urinary passages—experiments which, as their first essential condition, presuppose an accurate knowledge of the chemical composition of the calculus which is to be dissolved. Even the chemical composition of such calculi as are to be removed by an operation (lithotomy or lithotrity) has in addition to a scientific interest not rarely a practical one also, since it gives us the means of preventing by an appropriate internal treatment the formation of new concretions of the same composition in the patient operated on.

The chemical constituents of calculi are essentially the same as those which have already been considered under the head of urinary sediments, namely :

Uric acid and urates,  
Xanthin (uric oxide),  
Cystin,  
Calcic oxalate,  
Calcic carbonate,  
Calcic phosphate,  
Ammonio-magnesian phosphate,  
Protein compounds (fibrine, mucus),  
Urostealith,

as the principal constituents, with which are sometimes mixed small quantities of other substances (silica, clay, etc.).

Many urinary concretions consist chiefly of only one of these constituents, while others are mixtures of several of them which are either mixed together or form separate layers.

Since the properties and methods of detection of most of these substances have been already described, it will be sufficient here to point out the general process which must be followed in the analysis of such concretions, and refer to former sections for special tests.

If urinary *gravel* is to be examined, it is best to subject it to a preliminary microscopic examination, since its chemical com-

position can frequently be recognized from the form of its crystals, etc. For the chemical examination, it should be so prepared as to isolate the granules as completely as possible from adhering impurities, such as blood and pus, and they should be washed with distilled water. If the granules are large they should be powdered.

If a *calculus* is to be examined, it should be remembered that it not rarely consists of several layers of different chemical composition. It should, therefore, be sawed, or better, broken in pieces, and a portion of each layer, which appears by its looks to be different from the others, should be powdered and subjected to chemical examination. It is best in this case also to wash the powder with distilled water before the examination, in order to separate the infiltrated constituents which do not belong to the composition of the calculus.

I. If as accurate an analysis as possible is desired, and this method is to be recommended to those unskilled, it is best to begin by igniting a portion of the powder upon platinum foil over the spirit lamp. If the substance burns up completely, or only leaves, at the most, an unimportant residue, the calculus may consist of

Uric acid or urate of ammonium,  
Xanthin,  
Cystin,  
Protein substances,  
Urostealith.

In order to further determine of which of the above substances the concretion consists we proceed as follows :

We first test for uric acid. If an evident murexid reaction is obtained by treating the powder with nitric acid and ammonia, according to page 40, 8, and page 41, a, the concretion consisted of *uric acid* or *urate of ammonium*. These two may be distinguished by the fact that uric acid is very slightly soluble in boiling water, while urate of ammonium dissolves much more easily and in larger amount. On cooling it separates from this solution and evolves ammonia when treated with potassic hydrate. (See page 164, 3).

Calculi of uric acid are relatively very common, and may reach a very considerable size. They are usually colored (yel-



lowish, reddish, red brown), rarely white, usually have a smooth surface, and are tolerably hard.

Calculi of urate of ammonium are rare, usually small, of lighter (whitish or clay yellow) color, and more earthy in character.

If no murexid reaction is obtained, the combustible calculus may consist of

*Xanthin* (uric oxide). This substance dissolves in nitric acid without effervescence, and after the evaporation of this solution a bright citron-yellow residue is left, which is not colored red by ammonia, but is dissolved by potassic hydrate with a deep reddish-yellow color. (See § 5.) But since *guanin*, a substance recently discovered, but which has not yet been detected as a constituent of urinary concretions, gives a similar reaction, care should be taken before pronouncing that a urinary concretion consists of xanthin.

Calculi of xanthin are exceedingly rare, and at the present time only a few examples are known. They have a light brown (whitish to cinnamon brown) color, are tolerably hard, assume a waxy lustre on being rubbed, and consist of concentric amorphous layers which are easily separated.

Calculi of *cystin* are also quite rare: of dull yellow color, smooth surface, crystalline upon fracture, and with a waxy or fatty lustre. They are quite soft, easily scratched, and the powder has a soapy feel.

Chemically, cystin may be recognized from the following properties: It dissolves in ammoniac hydrate, and separates from this solution on slow evaporation in very characteristic crystals, which are regular hexagonal plates. It is also soluble in the mineral acids and separates from the hydrochloric acid solution on slow evaporation in the form of groups of diverging needles arranged in the shape of a wheel. It contains a considerable amount of sulphur. If, therefore, a concretion containing cystin is dissolved in potassic hydrate, and then boiled after the addition of a small amount of a solution of acetate of lead, a black precipitate of the sulphide of lead is formed, which gives to the mixture the appearance of ink. (See § 47.)

Calculi of *protein substances* (consisting of fibrine or blood coagula) are also very rare. They show no trace of crystallization,

evolve upon being ignited an odor of burnt horn, are insoluble in water, ether, and alcohol, soluble in potassic hydrate from which solution a precipitate is produced by acids, swell up in acetic acid, and are soluble in boiling nitric acid.

Calculi of *urostealith* are also very rare.\* When fresh they are soft and elastic, similar to caoutchouc. Upon being dried they become smaller, brittle, light brown to black in color, and are tolerably hard, but upon warming become softer again. On being heated they melt without volatilizing, swell up, and a very strong odor is evolved, which reminds one of a mixture of shellac and benzoin. Boiled in water they become soft without dissolving. They are easily soluble in ether; the amorphous *urostealith* left after evaporation of the ether becomes violet on being heated. They dissolve easily in potassic hydrate when heated, and are saponified. They dissolve in nitric acid with slight evolution of gas and without change of color: the residue is colored dark yellow by alkalies.

II. If the concretion is incombustible or leaves after ignition a considerable residue, it may consist of

- Urates of the fixed alkalies (sodium, potassium, calcium),
- Calcic oxalate,
- Calcic carbonate,
- Calcic phosphate,
- Ammonio-magnesian phosphate.

Calculi consisting solely of the *urates of sodium, calcium, and magnesium* are not of frequent occurrence, but these substances are sometimes contained in urinary calculi in larger or smaller amount, while the larger part of the calculus is made up of some other constituent, such as uric acid or urate of ammonium.

In order to determine whether such a calculus contains uric acid combined with these bases, the powder is boiled with distilled water and filtered while hot. The urates, which are more easily soluble in warm water than uric acid, pass through into the filtrate. This is evaporated and then ignited. The residue which remains contains the fixed bases. If this residue after ignition colors moistened turmeric paper brown, we may

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\* See Fl. Heller in s. Archiv, 1845, page 1, and W. Moore, Dublin Quarterly Journal, 1854, March.

conclude that it contains potassium or sodium—the latter may be recognized by the yellow color which it imparts to the blow-pipe flame. Magnesium and calcium remain behind as carbonates, when the residue has not been ignited too strongly, and are not, therefore, soluble in water, but dissolve in the dilute acids. If phosphate of sodium and ammoniac hydrate are added to this solution, the calcium and magnesium are precipitated as ammonio-magnesian and calcic phosphates. These two substances may then be separated from each other in the manner to be described below.

*Calcic oxalate* blackens on ignition on account of the combustion of the organic substances, but on being further ignited it readily becomes white and does not fuse. If strongly ignited, quick-lime is formed, which turns moistened turmeric paper brown. If gently ignited only calcic carbonate is formed which dissolves in hydrochloric acid with effervescence. If this solution is neutralized with ammonia no precipitate results, until oxalic acid is added, when calcic oxalate is again precipitated, and shows under the microscope its characteristic crystalline form. (See § 45, B.) The calcic oxalate is insoluble in boiling water and potassic hydrate; it is soluble in hydrochloric acid without effervescence.

Calculi of calcic oxalate are tolerably frequent, especially in children. They are either small, pale, and smooth—*hemp-seed calculi*—or are larger, of rough exterior, tuberculated, warty and colored on the surface, usually dark brownish or even blackish—*mulberry calculi*. These latter, by their rough exterior, usually irritate the urinary passages very much, and give rise to severe disease (inflammation, hemorrhage).

Calculi formed of *calcic carbonate* alone or containing it as the principal constituent are quite rare. They occur usually in large numbers in the same individual, have a whitish gray (rarely a dark, yellowish, or brownish) color, and usually present an earthy, chalky appearance. Their formation shows a lack of phosphoric acid in the urine. More frequently calcic carbonate occurs as a subordinate constituent of other calculi, mixed with calcic oxalate or the earthy phosphates.

Calculi of calcic carbonate blacken on ignition, since they usually contain a considerable amount of organic matter (mucus), but they easily burn white and are infusible. The residue after ignition has the same properties as that of calcic oxalate

calculi; it either remains calcic carbonate or is changed by strong ignition into quick-lime.

The very characteristic property of this calculus of dissolving in hydrochloric acid *with effervescence* renders its detection easy.

*Ammonio-magnesian phosphate* and (basic) *calcic phosphate* ordinarily occur mixed together as constituents of the same urinary concretion. Such calculi of the earthy phosphates indicate that the urine has for a long time been ammoniacal on account of the decomposition of urea within the urinary passages. They may reach a considerable size; they have usually a whitish color, and are more soft, porous, and chalky if the ammonio-magnesian phosphate predominates, or denser and harder if the calcic phosphate predominates.

Chemically they have the following characteristics: They do not char on being ignited, but melt to a white enamel-like mass, whence they have received the name of *fusible* calculi. Also, after strong ignition they do not have an alkaline reaction, whereby they may be distinguished from calculi of calcic oxalate and carbonate. They are soluble in hydrochloric acid, without effervescence both before and after ignition, and the hydrochloric acid solution of the ignited powder is precipitated by ammonia.

In order to separate these two constituents, the calcic and ammonio-magnesian phosphates, from each other, the ignited powder should be dissolved in dilute hydrochloric acid, and filtered. Ammonia is then added to the filtrate until the reaction is only very feebly acid, or the filtrate neutralized completely with ammonia until a turbidity appears, which is dissolved with a few drops of acetic acid. If oxalate of ammonium is now added, the calcium only will be precipitated as oxalate, while the ammonio-magnesian phosphate will remain in solution, and after filtering off the calcium precipitate may be obtained by saturating the filtrate with ammonia.

Calculi of *neutral calcic phosphate* resemble, in their physical and chemical properties, those of the earthy phosphates, but differ from them in not containing magnesium, so that their hydrochloric acid solution, after the precipitation of the calcium with ammonic oxalate, gives no further precipitate by saturating with ammonia. Such calculi are quite rarely seen. But according to my experience the occurrence of gravel, at least,

composed of calcic phosphate, is much more frequent than was formerly supposed, and I have observed a large number of such cases. I wish here to lay stress upon this observation, since the practising physician in most of these cases, without making an accurate examination of the gravel, considers it to consist of uric acid, and thereupon orders the use of alkalies, Vichy waters, etc.,—a procedure which, in these cases, instead of benefiting, only increases the evil.

Calculi do not always, however, have so simple a composition as those hitherto considered. Sometimes they contain several constituents. Thus there are calculi which consist of a mixture of uric acid and urates with the earthy phosphates; others which are mixtures of calcic oxalate and the phosphates. Calculi have been found, even, which contained at the same time uric acid, urate of ammonium, calcic oxalate, calcic phosphate, calcic carbonate, and ammonio-magnesian phosphate, six different constituents, therefore. These different constituents are sometimes mixed intimately with each other, and sometimes are deposited upon each other in different layers, which have evidently been formed at different times. This is explained by the fact that different sediments are deposited in the urine of the same patient at different times, and these adhere to any calculus present and increase its size. Thus, alternate layers of uric acid and urates occur, if in a case of long-continued urate diathesis the urine is sometimes strongly acid, so that the urates are decomposed, and uric acid itself is deposited, and sometimes slightly acid or neutral, so that the undecomposed urates are deposited upon the calculus. If the uric acid diathesis alternates with the oxalic acid, then alternate layers of uric acid and calcic oxalate are formed. Calculi very frequently met with, which consist of alternate layers of uric acid or calcic oxalate and the earthy phosphates, occur when the uric or oxalic acid diatheses periodically subside, and the urine becomes alkaline in the interval from the decomposition of urea, to which the abundant separation of mucus from the irritation of the calculus or the retention of urine, which sometimes occurs from the obstruction of the urethra or the exit of the bladder, contribute. The alternate layers of uric acid and calcic phosphate in a calculus are sometimes caused artificially by drugs, if the patient takes alkalies to antagonize the uric acid diathesis, since these

render the urine alkaline and cause a deposition of calcic phosphate which adheres to the calculus.

Most calculi have a nucleus which is sometimes a foreign body, upon which the urinary sediments deposit and form a crust. Every foreign body, which has in any way gotten into the urinary passages from without, or has been formed within the same, such as fibrine, or blood coagula, or clumps of mucus, may thus become the nucleus of a calculus. Retained gravel may also form the nucleus of a calculus. In the latter case the nucleus sometimes has a different chemical composition from the rest of the calculus, if during the formation of the latter the character of the sediment becomes changed. Sometimes it happens that a calculus has, instead of a nucleus, a vacant space in its interior; in this case, the nucleus consisted of mucus which later became dry. In rare cases it is noticed that the nucleus rattles within the stone, which is to be explained in the same way by the drying up of the mucus. Sometimes the calculus is made up of gravel or several small stones, which are united by a cement, and which sometimes have the same chemical composition as the calculus and sometimes a different one. All of these conditions must be taken into consideration when the chemical composition of the concretion is to be determined, and from this conclusions are to be drawn as to the probable processes which take place in its formation.

False urinary concretions also occur, and their recognition is of especial importance to the practising physician, when a hypochondriacal patient is brought to him laboring under the tormenting idea that he is suffering with a calculus or gravel. Thus it happens sometimes that sand or small stones, which accidentally get into the chamber-vessel, or are left in it after scouring it, are considered to be urinary concretions. They consist usually of silica, and may be distinguished from urinary concretions by their appearance and physical properties (great hardness), and if necessary by a chemical analysis by which both an absence of the characteristic properties of those substances which form urinary calculi is revealed, and upon analysis (ignition with sodio-potassic carbonate, and further treatment according to § 20) a considerable amount of silicic acid is detected in them, which is not found in true urinary concretions or only in traces.

## DESCRIPTION OF THE PLATES.

PLATE I., PLATE II., AND PLATE III., FIG. 1-4, FROM DR. FUNKE'S  
PHYSIOLOGICAL ATLAS.

### PLATE I.

*Fig. 1. Hippuric Acid*, prepared from normal human urine, recrystallized from water.

In addition to the ordinary prisms there are frequently formed, especially upon slow separation of the hippuric acid, crystals which are precisely similar to those of triple phosphate; such crystals are figured in the left lower third of the figure.

*Fig. 2. Uric Acid* of different forms, partly prepared by dissolving and recrystallizing chemically pure uric acid, partly by treating sediments of urates with acids, and partly by its spontaneous separation from the urine as a sediment.

The numerous forms of uric acid, from the simple rhombic plates with rounded obtuse angles most frequently seen to the rarer modifications, are easy to comprehend from the figure. The dumb-bells, shown in the left upper part of the figure, were artificially prepared, but they sometimes occur in spontaneous urinary sediments. Funke has always obtained them when he dissolved chemically pure uric acid in potassic hydrate, and precipitated it again under the microscope by concentrated hydrochloric acid.

*Fig. 3. Urinary Sediment* of uric acid, urate of sodium, and calcic oxalate, from the urine of a typhoid convalescent.

A common form of uric acid crystals in sediments consists of the figured, large, thick clumps united by twos at their base, which are made up of numerous, long, small, whetstone-shaped crystals, and which, as a rule, appear colorless. The beautiful, glittering, envelope-shaped crystals are calcic oxalate. The small, round, and angular dark granules, which are partly single and partly lie together in irregular groups and heaps, consist of urate of sodium which always appears in the urine in this molecular form. (Compare Plate II., fig. 1 and 2.)

*Fig. 4. Urinary Sediment* with epithelial casts and numerous



epithelial cells, taken after death with a catheter from the bladder of a patient who had died from typhoid fever.

The cylindrical casts figured consist of the epithelial lining of Bellini's tubes, whose round nucleated cells are plainly visible through a finely granular mass. The keel-shaped, caudate, and spindle-shaped cells which lie free come from the ureters and pelves and calices of the kidney.

*Fig. 5. Urinary Sediment* of hyaline tubular bodies, bladder epithelium, and mucous corpuscles, from a patient with acute miliary tuberculosis.

These casts, which are somewhat rarer than the foregoing, are so hyaline and homogeneous, that it is only with care that they can be distinguished from the surrounding fluid. In the case shown they are in places rendered more plainly visible by being filled with small granules of urate of sodium; their ends are sometimes swollen like a knob. Near them are seen roundish, long or polygonal, pavement epithelial cells from the bladder, most of which are plainly nucleated, and very granular mucous corpuscles.

*Fig. 6. Urinary Sediment* consisting of fibrinous casts, blood and pus corpuscles, and epithelial cells; albuminous urine of a typhoid patient, in whom the section showed a considerable inflammatory infiltration of the cortical substance of the kidneys.

The granular cylindrical bodies formed from an apparently granular molecular mass are coagula of fibrine (croupous exudation) from Bellini's tubes, whose form they have retained. Some contain blood and pus corpuscles enclosed in them, but these are seen in considerable amount free, the blood globules mostly swollen up like a little bladder, but partly with the central depression still plainly perceptible. The bipolar epithelial cells have already been described in connection with fig. 4.

## PLATE II.

*Fig. 1. Urinary Sediment* of urate of sodium from the heavy morning urine of a tuberculous patient.

The ordinary whitish, yellowish, or brick-colored deposit, which settles from a concentrated acid urine (especially in fevers) after cooling, consists almost exclusively of sodium urate, which separates in the form of granular molecules. When separated rapidly these granules are very fine and usually clumped together in the mossy groups shown in the figure.

Between these may be seen, when the urine has stood for some time (fig. 4.), a few fermentation spores, and (at the right lower edge) sometimes bladder epithelial cells which are usually very granular and appear wrinkled.

*Fig. 2. Urinary Sediment* consisting of urate of sodium, phosphates, and mucous coagula, after three days' standing.

The sodium urate has in this case separated in much larger darker granules and in larger heaps than in the previous figure. The uniformly granular membrane-like forms shown in the centre of the figure are fragments of the film consisting of the amorphous earthy phosphates with which urine undergoing decomposition exposed to the air is often covered. The smaller and broader curved bands, which consist of exceedingly fine dots and granules arranged in rows, are mucous coagula, which are frequently found in acid urine and may be easily confounded with the casts above mentioned. In addition fermentation spores may be found here also partly arranged in rows and plates (as at the lower edge), and single very granular mucous corpuscles. .

*Fig. 3. Urinary Sediment* consisting of triple phosphate and numerous mucous corpuscles, from the freshly passed alkaline urine of a patient with catarrh of the bladder.

The crystals of ammonio-magnesian phosphate have different forms, but they are always easy to recognize without crystallographical or chemical analysis. The mucous corpuscles are rather small, much contracted, and granular, and usually with their edges united so as to form large groups like a coat of mail.

*Fig. 4. Urinary Sediment* consisting of urate of sodium, uric acid, and fermentation spores, from a urine undergoing acid fermentation after standing.

Every normal and almost every acid pathological urine undergoes acid fermentation upon long standing. With the increase of the acid reaction there form in it the small nucleated fermentation spores, which increase by budding, and thus form simple and branching rows like those shown. At the same time the yellow uric acid crystals of the simple forms shown in the figure separate in gradually increasing amount from the urate of sodium which is present in the ordinary form. In addition to these, small octahedral crystals of calcic oxalate frequently appear (as, for example, at the right upper edge).

*Fig. 5. Urinary Sediment* consisting of triple phosphate crys-

tals and urate of ammonium, from a urine which has undergone alkaline fermentation in a case of paralysis of the lower extremities in consequence of a spinal affection.

The triple phosphate crystals figured have the most common form which occurs in every decomposed urine. The urate of ammonium separates at first in the form of very fine molecules, from which the gradually increasing, dark, strongly refracting globules develop, which are later covered with fine spiculæ of varying length, like a thorn apple

*Fig. 6. Nitrate of Urea* precipitated from very concentrated human urine by nitric acid.

### PLATE III.

*Fig. 1. Urinary Sediment* consisting of uric acid crystals, from the urine of a girl suffering with *acute rheumatism* (during the menstrual period).

In addition to the yellowish-brown rhombic tables, kegs, whetstones, etc., of uric acid, which are mostly united together in groups and bunches, and represent the most common forms of sediment so frequently seen in the shape of a golden, glittering, granular sand, there are numerous distinctly yellow blood corpuscles, which are swollen, bladder-shaped, and of very different size.

*Fig. 2. Human Blood Corpuscles* treated with water.

The gradual change produced in blood corpuscles is shown in the figure beginning at the left and increasing toward the right. The first result of the action of water is that the cells swell up, become more lenticular and finally spherical, while the central depression becomes more nearly level and is finally arched; this is necessarily accompanied by a shortening of the transverse diameter of the disk. They appear, therefore, smaller, and the shadow in the centre grows pale and disappears, and the more a spherical shadow on the edge appears, the less clearly does the cell standing upon its edge show the lenticular shape. By the further action of the water the cells become fainter and paler, and more difficult to distinguish from the surrounding fluid, since their contents, by the imbibition of water, obtain the same refracting power as the external fluid; they appear only as exceedingly delicate hyaline bladders, and finally become totally invisible. If a concentrated solution of a neutral salt is then added, they appear in the distorted, angu-

lar, and ragged forms seen in the lower right-hand corner of the figure.

*Fig. 3. Pus Corpuscles.*

The lower half of the figure shows the normal pus corpuscles as round, pale, delicate, granular bladders of somewhat varying size, of which some permit a single round eccentric nucleus to be seen, but others a nucleus several times divided. As the figure shows, some of the corpuscles are very distinctly limited by sharp lines, while others show only a delicate contour as if washed. The upper half of the figure shows the action of acetic acid upon the pus corpuscles. They swell up and their surface becomes smooth and so hyaline that the contour can sometimes no longer be distinguished; thereby the nuclei of different number and form become visible, partly as single round elongated, biscuit or horseshoe-shaped bodies, and partly double or triple and quadruple in the different forms and grouping as shown in the figure, as if they were formed by splitting of the single ones.

*Fig. 4. Cystin*, obtained from a vesical calculus, and recrystallized from ammoniac hydrate.

*Fig. 5 and 6* illustrate the most important and most frequently occurring organized elements which are found in the urinary sediment in cases of cancer of the bladder.

For the special explanation of the individual figures and their importance consult § 115.

#### PLATE IV.

##### *Vogel's Urinary Color Table.*

Fig. 1. Pale yellow.	Fig. 6. Red.
“ 2. Light yellow.	“ 7. Brownish red.
“ 3. Yellow.	“ 8. Reddish brown.
“ 4. Reddish yellow.	“ 9. Brownish black.
“ 5. Yellowish red.	

Hæmatin in acid alcoholic solution shows, in addition to the two absorption bands between C and D, figured in Plate IV., when moderately diluted, two others which are feeble, disappear more quickly on further dilution, and are, therefore, not characteristic.

Methæmoglobin shows, when the solution is not alkaline, the same absorption bands as hæmatin. (Page 181.)

The spectrum of oxyhæmoglobin shows the two very characteristic absorption bands described on page 179.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.



Fig. 6.





Fig. 1.

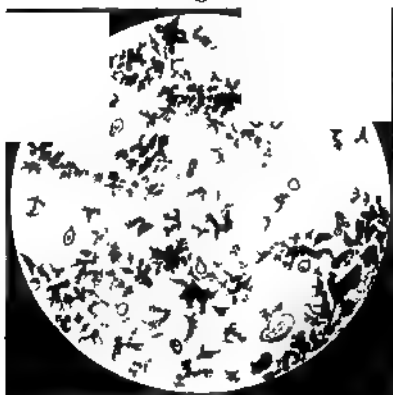


Fig. 2.

Fig. 3.



Fig. 4.

Fig. 5.



Fig. 6.







Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

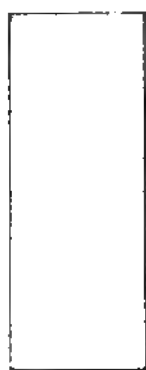
Fig. 5.

Fig. 6.





*1 Pale yellow.*



*2 Bright yellow*



*3 Yellow.*

*4 Reddish yellow.*

*5 Yellowish-red*

*6 Red.*

*7 Brownish-red*

*8 Reddish brown*

*9 Brownish-black.*

**Table of colors of the Urine.**

*Haematin.*

*Haemoglobin.*



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